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Deranged Survival, Development and Reproductivity of the Egyptian Cotton Leafworm *Spodoptera littoralis* Boisd (Lepidoptera: Noctuidae) by Fluoromevalonate

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Original Research Article

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Abstract: The cotton leafworm, *Spodoptera littoralis* is a serious pest of cotton and field crops in Egypt and many countries in the world. The objective of the current investigation was to evaluate the effects of Fluoromevalonate (FMev), on survival, development and reproductivity of this pest. For this purpose, four doses (100, 50, 25 and 5 µg/larva) had been topically applied onto the newly moulted 5th and 6th (last) instar larvae. A weak lethal potency was recorded for FMev against all developmental stages. After treatment of 5th and 6th larval instars, LD_{50} values were 42.03 and 629.20µg/larva, respectively. The growth of larvae was inhibited after treatment of 5th instar larvae, but enhanced after treatment of 6th instar larvae. The larval duration was significantly shortened, but the pupal duration was slightly or remarkably prolonged. The pupation and adult emergence had been inhibited. Treatment of 6th instar larvae with the three higher doses of FMev resulted in the production of malformed pupae. Depending on the present results, FMev failed to exhibit an anti-JH activity, but exhibited a powerful anti-gonadotropic activity against *S. littoralis*, since complete sterilization was recorded.
Keywords: fecundity, fertility, growth, metamorphosis, morphogenesis, mortality, oviposition.

INTRODUCTION

As a result of excessive and improper uses of the conventional insecticides against insect pests, several adverse impacts have been recorded on the human health and beneficial animals as well as serious toxicological problems to the environmental systems [1-6]. Therefore, eco-friendly control materials have received global attention in recent years as alternative for these hazardous insecticides.

These alternative compounds should be characterized with lower toxicity to non-target organisms, efficiency at low concentrations [7, 8] and biodegradable into harmless compounds [4, 9, 10].

The juvenile hormone (JH) is necessary for insect development throughout the immature stages [11]. In addition, JHs play important roles in several other physiological processes, such as reproduction, diapause, behaviour, polymorphism, migration, metabolism and innate immunity [12-21]. Since few decades, the use of insect juvenile hormone analogues (JHAs), or insect growth regulators (IGRs) in general, has been considered as a possible alternative of the conventional insecticides for controlling the insect pests [22]. Because of their desirable characteristics, such as low toxicity, high selectivity, low impact on people and natural enemies of pests, less environmental pollution, IGRs are used to control various insect pests [23-25]. They are regarded as a 'third generation of insecticides' or biorational pesticides with different mode of action [26]. Precocenes (anti-JH compounds) and their synthetic mimics received a great attention by entomologists owing 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 [27-31].

Bede *et al.* [32] demonstrated that the design of JH mimics or anti-JH agents is an effective strategy for insecticide discovery. On the other hand, compounds with anti-JH activity are considered as new representatives of IGRs lacking some disadvantages of juvenoid-type chemicals [33, 34]. These anti-JH chemicals are potentially efficacious for control of the major insect pests where most of the damage is caused by larval stage [35]. 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 [11, 36, 37, 38]. Fluoromevalonate (FMev) was known for its hypocholesteremic activity in mammals [39]. As reported by Sánchez *et al.* [40], FMev is a competitive inhibitor of mevalonate diphosphate

decarboxylase and exhibits an inhibitory effect on cholesterol biosynthesis, cell proliferation and cell cycle progression in human leukaemic HL-60 and MOLT-4 cells. In agricultural purposes, FMev was reported to exhibit anti-JH activity against several species of Lepidoptera, such as *Manduca sexta*, *Samia cynthia*, *Phryganidia californica*, *Galleria mellonella*, *Spodoptera exigua*, and *Heliothis virescens* [41-43]. Also, FMev was reported to exhibit anti-JH activity against the American cockroach *Periplaneta americana* through the inhibition of JH III biosynthesis in CA [44].

The cotton leafworm, *Spodoptera littoralis* has been considered as a destructive lepidopterous pest of cotton and various field crops all over the year in Egypt [45-48] as well as tropical and temperate zones of the old world [49]. To control the attacks of *S. littoralis*, several types of conventional insecticides have been used over the past 40 years [50]. The use of these insecticides has led the development of resistance against many registered pesticides making their control even more difficult [51-56]. The objective of the present study was to assess the disruptive effects of FMev on survival, growth, development, metamorphosis and reproductive potential of the dangerous insect pest *S. littoralis*.

MATERIALS AND METHODS

Experimental insect

A culture of the Egyptian cotton leafworm, *Spodoptera littoralis* (Lepidoptera: Noctuidae) was established in Department of Zoology and Entomology, Faculty of Science, Al-Azhar University, Cairo, under laboratory controlled conditions (27±2^{o}C, 65±5% R.H., photoperiod 14h L and 10h D). The culture was originated by a sample of pupae from the susceptible strain maintained for several generations in Plant Protection Research Institute, Agricultural Research Center, Giza, Egypt. Rearing procedure was carried out according to Ghoneim [57] and improved by Bakr *et al*. [58]. 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 administration

Fluoromevalonate (FMev) (tetrahydro-4-fluoromethyl-4-hydroxy-2H-pyran-2-one) was kindly provided by Dr. Heba Hassan, Prof. at Plant Protection Research Institute, Giza, Egypt. 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 a day after treatment all treated and control insects were observed daily to record all criteria of study.

Criteria of study

Toxicity, affected growth, development, metamorphosis and morphogenesis

Toxicity of FMev was detected by mortality (%) of larvae, pupae and adults. LD_{50} values were calculated using the total mortality by Microsoft office Exel, 2007, according to Finny [59]. Coefficient of growth was calculated according to El-Ibrashy and Aref [60] as follows: Maximal body weight (mg)/ duration (in days) for each larva. Developmental duration was calculated in mean days±SD using Dempster's equation [61] and the developmental rate was determined using Richard's equation [62]. 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 into Petri dishes to count eggs.

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* was calculated according to Toppozada *et al.* [63], 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 [64] for the test significance of difference between means.

RESULTS

Toxic effect of FMev on *S. littoralis*

After topical treatment of the newly moulted 5th instar larvae, toxicity of FMev was expressed in mortality among larvae, pupae and adults. According to data of Table 1, different mortalities were recorded among the treated larvae (40.0, 36.0, 60.0 and 12.0% mortality, at 100, 50, 25 and 5 µg/larva, respectively, *vs*. 0% mortality of control larvae). Also, the moulted 6th instar larvae suffered a toxic action of FMev only at the highest dose (13.3% mortality, *vs*. 0% mortality of control larvae). The pupal mortality was observed only at the higher two doses. The adult mortality was observed only at the highest dose. LD_{50} value was found 42.03µg/larva. The same table contains data of FMev toxicity after treatment of 6th instar larvae. Depending on these data, FMev exhibited a toxic effect on larvae and pupae only at the higher two doses. Adult females were subjected to extended toxic effect of FMev only at the highest dose level. LD_{50} value was calculated in 629.20µg/larva. Thus, *S. littoralis* was more sensitive to FMev toxicity when treated as 5th instar larvae.

Effect of FMev on growth of *S. littoralis*

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 moulted 6th instar larvae were assorted in Table 2. Depending on these data, max. wt of treated 5th instar larvae significantly decreased, at the higher two doses (102.8±17.5 and 103.7±5.8 mg, at 100 and 50µg/larva, respectively, compared to 119.0±38.9 mg of control larvae). In contrast, max. wt remarkably increased at the lower two dose levels (138.3±8.7 and 151.20±17.6 mg, at 25 and 5 µg/larva, respectively, compared to 119.0±38.9 mg of control larvae). FMev exerted a strong inhibitory action on the larval growth, since the CG was considerably regressed, especially at the higher three dose levels. With no exception, FMev enhanced the successfully moulted 6th instar larvae to attain increasing max. wt in a dose-dependent course. In a similar trend, CG was pronouncedly induced (for detail, see 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. On the basis of these data, the max.wt increased, in no certain trend. This increasing max. wt was statistically significant at the doses 50 and 25 µg/larva (745.9±128.2 and 349.8±78.2 mg, respectively, *vs*. 295.6±31.8 mg of control larvae). On the other hand, FMev remarkably enhanced the treated larvae to grow with higher CG (118.9±18.9, 189.3±35.2, 088.2±23.7 and 081.6±12.6, at 100, 50, 25 and 5 µg/larva, respectively, *vs*. 074.1±9.5 of control larvae).

Effect of FMev on development and metamorphosis of *S. littoralis*

Affected duration and development

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 significantly shortened, especially at the higher two doses (1.0±0.0 and 1.0±0.1 days, at 100 and 50 µg/larva, respectively, in comparison with 1.9±0.3 days of control larvae). Also, duration of the moulted 6th instar larvae was considerably shortened; especially at the higher two doses (4.0±0.7 and 4.1±0.6 days, at 100 and 50 µg/larva, respectively, in comparison with 4.5±0.5 days of control larvae). As obviously shown in Table 3, topical application of FMev onto last instar larvae resulted in an abbreviation of larval duration, especially at the higher two doses (2.8±0.8 and 4.1±0.3 days, at 100 and 50 µg/larva, respectively, *vs*. 4.2±0.4 days of control larvae).

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 (7.7±3.1 and 7.9±2.8 days, at 100 and 50 µg/larva, respectively, *vs*. 4.2±0.4 days of control pupae). Also, 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. The developmental rate of pupae was regressed after treatment of 5th instar larvae (Table 4) and 6th instar larvae (Table 5), regardless the dose level of FMev.

Impaired metamorphosis and morphogenesis

Precocious metamorphosis

According to the data of 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. In contrast, data of Table 5 revealed that FMev exhibited a JH-like activity against the treated last instar larvae; since larval-pupal intermediates were produced at the higher two doses (20 and 10% intermediates, at 100 and 50 µg/larva, respectively, Fig.1).

Pupation process

Depending on the data of Table 4, FMev exerted an inhibitory action on the pupation after treatment of 5th instar larvae with the higher three doses (43.5, 48.5 and 69.5% pupation of treated larvae, at 100, 50 and 25 µg/larva, respectively, *vs*. 100% pupation of control larvae). 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 (90 and 95% pupation of treated larvae, at 100

and 50 µg/larva, respectively, *vs*. 100% pupation of control larvae).

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 a morphogenic efficiency on pupae, after treatment of 6th instar larvae only with the higher three doses, since some malformed pupae had been produced (50, 10 and 5% abnormal pupae, at 100, 50 and 25 µg/larva, respectively, *vs*. 0% abnormality in control pupae). As clearly shown in Fig. 2, some features of the impaired pupation program appeared in dwarf-sized pupae which failed to metamorphose into adults.

Adult emergence

After treatment of 5th instar larvae only with the higher two doses, FMev exerted a blocking action on the adult emergence (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).

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 mortality 5th instar	Larval mortality 6th instar	Pupal mortality	Adult mortality	Total mortality	LD_{50} (µg/ larva)	Larval mortality	Pupal mortality	Adult mortality	Total mortality	LD_{50} (µg/larva)
100	40.0	13.3	15.4	9.1	60.0	42.03	20.0	10.0	11.1	36.0	629.20
050	36.0	00.0	12.5	0.0	44.0		12.0	9.1	00.0	20.0	
025	60.0	00.0	00.0	0.0	60.0		00.0	00.0	00.0	00.0	
005	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	

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
050	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
025	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
005	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).

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
050	745.9±128.2 c	4.1±0.3 a	189.3±35.2 c
025	349.8±78.2 b	4.3±0.6 a	088.2±23.7 b
005	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.

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
050	0	48.5	7.9±2.8 a	12.80	0	66.6
025	0	69.5	7.5±3.3 a	13.33	0	100
005	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.

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
050	10	95.5	7.39±1.4 a	13.53	10	45.5
025	00	100	8.00±0.8 c	11.95	05	50.1
005	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.

Fig-1: 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

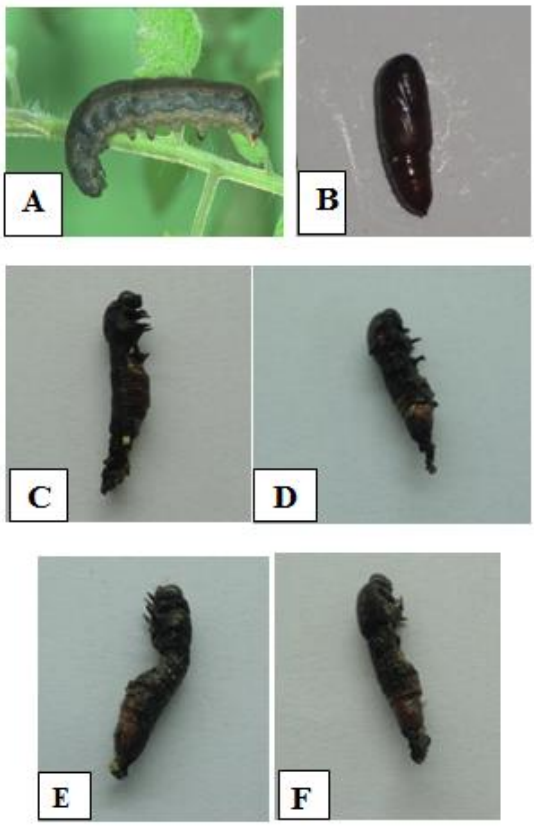

Fig-2: Larval-pupal intermediates of *S. littoralis* as features of disturbed metamorphosis program after treatment of last instar larvae with the higher two doses of FMev. (A): Normal last instar larva. (B): Normal pupa. (C, D, E & F): Various larval-pupal intermediates.

Effect of FMev on the reproductive potential of *S. littoralis*

After topical application of FMev doses onto the 5th instar larvae, data of the most important criteria of the reproductive potential were assorted in Table 6. After topical application of FMev doses onto the 6th instar larvae, data of the reproductive parameters were assorted in Table 7.

Oviposition rate

Depending on data of Table 6, oviposition efficiency of the adult females was considerably prohibited after topical treatment of 5th instar larvae with FMev (75, 85, 90 and 90% oviposition, at 100, 50, 25 and 5 µg/larva, respectively, *vs*. 100% oviposition by control females). 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).

Reproductive capacity

The functional compartments of reproductive capacity taken in consideration herein were fecundity (mean eggs/♀) and fertility (hatchability= hatching% of laid eggs). According to the data of Table 6, FMev exerted a strong suppressive effect on fecundity after treatment of 5th instar larvae with different doses (135.5±30.5, 336.5±32.1, 338.7±32.5 and 208.5±98.1 eggs/♀, at 100, 50, 25 and 5 µg/larva, respectively, *vs*. 943.3±85.5 eggs/control ♀). Similarly, FMev exerted drastically reducing action on fecundity after treatment of 6th instar larvae (098.2±18.0, 283.8±33.2, 602.8±149.4 and 104.6±18.9 eggs/♀, at 100, 50, 25 and 5 µg/larva, respectively, *vs*. 1259.2±120.3 eggs/control ♀, Table 7). With no exception, all eggs failed to hatch, regardless the larval instar under treatment and FMev dose. In other words, FMev caused complete sterility in *S. littoralis*. Therefore, no incubation period could be measured.

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

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	100	---
050	85	336.5±32.1 c	00	100	---
025	90	338.7±32.5 c	00	100	---
005	90	208.5±98.1 c	00	100	---
Control	100	943.3±85.5	98.8	---	3.5±0.5

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

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	0	100	---
050	70	283.8±33.2 c	0	100	---
025	81.5	602.8±149.4 c	0	100	---
005	83.8	104.6±18.9 d	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)

DISCUSSION

Affected survival of *S. littoralis* by FMev

There are many reported results on the 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 [65, 66]. Precocenes exhibited larvicidal effects on the Colorado potato beetle *Leptinotarsa decemlineata* [67]. A toxicological effect of PII was reported by Abdullah [68] against larvae of the red palm weevil *Rynchophorus ferrugineus*. Also, PII exhibited larvicidal and pupicidal effects on the grey flesh fly *Parasarcophaga dux* [69]; larvicidal effect on the lepidopterous pest *Pericallia ricini* [70]; and larvicidal effect on the Asian tiger mosquito *Aedes albopictus* [71]. 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) [72] and some synthesized analogues of FMev (tetrahydro-4-fluoromethyl-4-hydroxy-2H-pyran-2-one) [73] against the mulberry silkworm *Bombyx mori*. Our results were, to some extent, in agreement with those reported results, but FMev exhibited a weak toxic potency against larvae, pupae and adults of *S. littoralis*. However, the larval deaths of *S. littoralis*, in the present study, might be attributed to the prevention of moulting larvae to swallow air for splitting the old cuticle and expand the new one during ecdysis [74]. Also, these larval deaths might be due to the prevented feeding and continuous starvation of the insect [75]. The pupal deaths can be

directly related to the hormonal activity of the tested compound or might be to other causes, such as suffocation, bleeding and desiccation due to imperfect exuvation, failure of vital homeostatic mechanisms, *etc*. [76]. 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 [77].

The reported LD_{50} (or LC_{50}) values of anti-JH compounds are variable in different insects. For examples, LD_{50} of PII against the red cotton stainer *Dysdercus koenigii* had been found 85.46 and 82.37 mgl^{-1} against 4th and 5th instar nymphs, respectively [78]. 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 [71]. LC_{50} values of PII and PI against the booklice *Liposcelis bostrychophila* were calculated in 30.4 and 64.0$\mu g/cm^2$, respectively [79]. LC_{50} of PI against the cat flea *Ctenocephalides felis* was estimated in 10.97 ppm [80]. 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 [10]. In the current study, LD_{50} values were estimated in 42.03 and 629.20µg/larva, after treatment of 5th and 6th instar larvae, respectively. Thus, the 5th instar larvae were more sensitive to FMev than 6th instar larvae. It may be important to mention that variable LD_{50} 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 level, method and time of treatment, as well as the experimental conditions.

Growth disturbance in *S. littoralis* by FMev

Very few studies have examined the effects of anti-JH compounds on the growth of larvae in insects. Among these few studies, Roberto *et al*. [81] 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 *Anopheles stephensi* [65, 66]. After feeding of caterpillars of the tobacco hornworm *Manduca sexta* on a diet supplemented with HMG-CoA reductase inhibitors, Fluvastatin, Lovastatin or Pitavastatin, the growth rate of treated larvae was significantly slow [10]. Results of the present study on *S. littoralis* were, to some extent, in agreement with those reported results, since FMev exerted strong inhibitory action on the growth of treated 5th instar larvae whose coefficient of growth was considerably regressed. However, FMev exerted a diverse action on the maximal body weight, after treatment of 5th instar larvae, but the body weight remarkably increased at the lower two doses. To understand the growth inhibition of *S. littoralis*, in the current study, FMev might affect the tissues and cells undergoing mitosis [82]. Also, FMev might exert an inhibitory action on the haemolymph and fat body protein contents, as suggested by Lange *et al*. [83] 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 maximal body weight and enhanced their growth. This promoting action of FMev on the larval growth cannot be interpreted right now!!

Deteriorating effects of FMev on development and metamorphosis of *S. littoralis*

Affected development

The developmental rate of an insect stage is usually reversely related to the developmental duration, i.e. shorter duration indicates faster rate and *vice versa*. As seen in the currently available literature, the larval duration in several insect species had been prolonged as a response to the action of different anti-JH compounds. For examples, Bowers and Aldrich [84] 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 [85]. Treatment of 6th instar larvae of the lawn armyworm *Spodoptera mauritia* with PII resulted in prolongation of duration in last larval instar [86, 87]. The nymphal period of the grasshopper *Aiolopus thalassinus* was prolonged after topical application of PIII onto 5th instar nymphs [88]. 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 [89, 90]. After treatment of 4th instar nymphs of *D. koenigii* with PII, duration of the successfully moulted 5th instar nymphs was prolonged [78]. Apart from precocenes, Farag and Varjas [42] recorded a prolongation in the larval duration after topical application of FMev onto the three latter instars of fall webworm *Hyphantria cunea*. Similar results of prolonged larval duration were reported in *B. mori* by KK-22 (phenylimidazoles) [72, 92]. 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 [93].

Results of the current investigation disagreed with the previously reported results, since topical application of FMev onto 5th instar larvae resulted in a remarkably shortened larval duration, especially at the higher two doses. Also, duration of the successfully moulted 6th instar larvae was considerably shortened. In a similar trend, the larval duration was shortened after treatment of 6th instar larvae, especially at the higher two doses. 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 [69]; the flesh fly *Sarcophaga*

ruficornis after treatment of the last instar larvae with PI, PII or PIII [94]; the house fly *Musca domestica* after treatment of the larvae with PII [95]; *B. mori* after treatment of the 3rd and 4th instars with the imidazole compound SSP-11 [96]. On the other hand, topical application of FMev onto the 5th or 6th instar larvae of *S. littoralis*, in the present study, resulted in a slight or remarkable prolongation of the pupal stage, regardless the dose level. Also, the developmental rate of the pupae was unremarkably regressed. As far as our literature survey could ascertain, no information was available for the effects of anti-JH compounds on the pupal duration or developmental rate.

To explicate the shortened larval duration of *S. littoralis*, in the current investigation, it might 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 [97]. 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 [33, 72]. In addition, FMev might exhibit a delaying effect on the pupal transformation into adults [74]. 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 [98].

Impairment of metamorphosis and morphogenesis

Inhibited pupation and adult emergence: No information is available for the inhibitory effects of anti-JH compounds on the pupation rate in insects. In the present study on *S. littoralis*, the pupation rate was drastically regressed after treatment of penultimate instar larvae with the higher three doses (100, 50 and 25 µg/larva) or after treatment of last instar larvae with the higher two doses. However, the present result was consistent with the reported inhibitory effects of some JHAs or other IGRs on the pupation rate in various insects, such as the diamondback moth *Plutella xylostella* by hexaflumuron [99]; *S. littoralis* by novaluron [100]; the lesser mulberry pyralid *Glyphodes pyloalis* by lufenuron [101]; the pink boll worm *Pectinophora gossypiella* [102] and the olive leaf moth *Palpita unionalis* [103] by novaluron. To understand the regression of pupation rate 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. In addition, FMev might block the release of morphogenic peptides, causing alteration in both ecdysteroid and juvenoid titers [104]. A suggestion of Gaur and Kumar [105] may be appreciated. FMev might disrupt the ecdysteroid metabolism or might alternatively act directly to inhibit the release of ecdysis-triggering hormone.

Only scarce studies have examined the effects of anti-JH compounds on the adult emergence in insects. Inhibition of adult emergence in *S. ruficornis* was recorded after larval treatment with PII [106]. KK-42 (a terpenoid imidazole) was reported to inhibit the adult emergence of *B. mori* when applied to the newly formed pupae [107]. In the present study on *S. littoralis*, FMev exhibited a blocking effect on the adult emergence, after treatment of 5th instar larvae with the higher two doses. Moreover, topical application of FMev onto 6th instar larvae led to impeded adult emergence, in a dose-dependent manner. 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 has leads to 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 resulting in failure of the adult emergence [108]. In other words, FMev might disturb the adult eclosion hormone release and/or inhibition of the neurosecretion [109, 110]. 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 [111, 112].

Disturbed metamorphosis: In the current study, FMev failed to induce the precocious pupation or metamorphosis of *S. littoralis*. Thus, this compound did not exhibit anti-JH activity against the present insect. This result 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 [113]. Moreover, no precocious metamorphosis could be induced in 3rd and 4th instar larvae of the lepidopteran *Cydia pomonella* [114]. FMev doses were topically applied once onto 2-day old larvae of the penultimate instar of gypsy moth *Lymantria dispar*. All treated larvae developed normally, with few exception of incomplete moulting to the last instar [115]. In addition, other anti-JH compounds failed to induce precocious metamorphosis in some insects, such as the sunn pest *Eurygaster integriceps* after treatment with PI [116], *S. mauritia* after treatment with PII [86], *B. mori* after treatment with EMD or its analogues [72] or the synthesized

compound (S)-(+)-FMev [73] and *S. gregaria* after treatment with PII [117].

Our result was inconsistent with those reported results of precocious pupation or metamorphosis in several lepidopterous species, as a response to the same compound, FMev, such as *M. sexta*, *Samia cynthia*, *Phryganidia californica*, *Galleria mellonella*, *Spodoptera exigua*, *S. littoralis* and *Heliothis virescens* [41, 42]. Also, the 3rd instar larvae of *M. sexta*, treated with FMev, exhibited visible symptoms of JH deficiency following the moult to 4th instar, such as production of premature pupae [118]. Edwards *et al*. [44] reported an anti-JH activity for FMev against the American cockroach *Periplaneta americana via* the inhibition of JH III biosynthesis. Apart from FMev, various anti-JH compounds induced precocious metamorphosis in different insects, such as PII against the flesh fly *Neobellieria bullata* [119], PII against the lepidopterous pest *Pericallia ricini* [70] and a synthesized 3-pyridine derivative against *B. mori* [93]. The failure of FMev to induce precocious metamorphosis of *S. littoralis*, in the current study, might be explained by its inability to affect the larval JH levels [118]. Some authors [11, 120, 121] 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 [86, 122].

On the contrary, FMev exhibited a JH-like activity, on last instar larvae of *S. littoralis*, in the current investigation, since non-viable larval-pupal intermediates had been produced; at the higher two doses (100 and 50 µg/larva). These mosaic creatures were unusual and died after formation. 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 resulted in formation of larval-pupal intermediates [89, 90]. Khafagi and Hegazi [123] 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 intermediates were produced in *S. mauritia* after treatment with EMD [43]. In addition, the formation of larval-pupal intermediates was recorded in some insects as response to some precocenes [70].

The production of larval-pupal intermediates, in the present study, indicated a disturbing potency of FMev on the metamorphosis program of *S. littoralis*. This result can be interpreted by the impairment of hormonal regulation of pupation program [109]. In other words, 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 [124]. 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 [125]. Wilson [111] discussed the JH action on the molecular basis and concluded 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 directly 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 the impaired development, like larval-pupal intermediates, are the end results [112].

Deranged morphogenesis: In the present study on *S. littoralis*, FMev failed to affect the morphogenesis program after treatment of penultimate instar larvae, since no deformed pupae or adults had been observed. On the contrary, treatment of last instar larvae with FMev resulted in the impairment of pupation program, since morphologically abnormal pupae had been produced at the higher three doses (100, 50 and 25 µg/larva). Some symptoms of the program failure appeared in non-viable dwarf-sized pupae which died without metamorphosis 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 [126, 127]. FMev induced various morphogenetic abnormalities and death before pupation in *S. mauritia* [128]. 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 [129]. Topical application of PIII onto eggs or 5th instar nymphs of *A. thalassinus* resulted in some prothetelic morphogenic disturbances [77]. Production of abnormal puparia was recorded in *S. ruficornis* after administration of PI, PII or PIII to the last instar larvae [94]. Treatment of *S. litura* larvae with PI, PII or ethoxyprecocene (a synthetic analog of P II) resulted in the production of abnormally formed pupae [99]. Puparial malformations were observed in *P. dux* after topical application of PII onto the 3rd instar larvae [69]. Treatment of *M. domestica* maggots with PII led to the formation of abnormal puparia [95]. Larval treatment of *E. integriceps* with PI led to the production of some morphological abnormalities [38]. To understand the impairment of the pupation program in *S. littoralis*, as caused by FMev in the present study, FMev might

suppressed the chitin synthesis and prevented the normal deposition of new cuticle during apolysis leading to the production of pupal deformities [130].

Disrupted reproductive potential of *S. littoralis* by FMev

Reproduction in insects is controlled mainly by JH, which is also responsible for the protein metabolism needed for the egg maturation [131]. On the other hand, ecdysteroids have essential functions in controlling the processes involved in insect reproduction, *viz*., vitellogenesis, ovulation of matured eggs and spermatocyte growth [132, 133]. Generally, effects of IGRs on the insect reproduction can be grouped into: reproductive behaviour, oviposition, egg hatchability (ovicidal and embryocidal), and sterilization of adults [134].

Inhibited oviposition efficiency of adult females

In insects, the oviposition rate can be used as an indicator for the oviposition efficiency [131]. As recorded by many studies, oviposition rate of different insect species has been regressed by various IGRs [135-139]. 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 [140]. Exposure of the vinegar fly *Drosophila melanogaster* females to 0.14 µmol of PI resulted in remarkably regressed oviposition rate [37]. Larval treatment of *E. integriceps* with PI led to decreasing egg laying rate [38]. Results of the present study were in accordance with these reported findings, since the oviposition rate of adult females of *S. littoralis* was dramatically regressed after treatment of 5th or 6th instar larvae with different doses of FMev, in a dose-dependent course. 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 [141].

Reduced reproductive capacity

Fecundity

In the present study, FMev exhibited strong anti-gonadotropic activity against *S. littoralis*, since the female fecundity was drastically suppressed after treatment of 5th or 6th instar larvae. This result was, 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* [114] and the ticks *Boophilus microplus* [142] and *O. moubata* [140]. 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 (0.125 and 0.0625 mg) onto 3rd instar larvae of *P. dux* caused inhibition of the female natality [69]. Exposure of 5th instar nymphs of *N. lugens* to different doses of PII resulted in fecundity reduction, in a dose-dependent manner [143]. After treatment of *E. integriceps* nymphs with PI, fecundity of adult females was reduced [38]. Repeated daily topical application of PI or PII onto *S. littoralis* larvae reduced the fecundity of its parasitic wasp *M. rufiventris* [144]. Apart from precocenes, application of the anti-JH compound H17 reduced the fecundity of *L. decemlineata* [145]. 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* of which males were treated with PII and ethoxyprecocene but the fecundity did not differ statistically from that of the control groups [146].

In order 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 [147], while ecdysone, produced in the egg follicles, induces yolk protein mRNA expressed in the fat body [148-150]. In addition, the fecundity inhibition in *S. littoralis* might be due to the interference of FMev with one or more processes from the ovarian follicle development to the egg maturation. In addition, FMev might cause some disorders in the ovaries, including cell death in the germarium, resorption of oocytes in the pre-vitellarium and vitellarium [151, 152]. FMev might inhibit the synthesis and metabolism of proteinaceous constituents during oogenesis [153]. FMev might exert an inhibitory action against the function of authentic gonadotropic hormone (JH in adults) responsible for the synthesis of vitellogenins and vitellogenesis [154].

Fertility: According to the available literature, fertility (hatchability) of some insects had been reduced as a result of larval treatments with a number of anti-JH compounds. For examples, topical application of PIII onto eggs or 5th instar nymphs of *A. thalassinus* led to sterility of adult females [77]. After treatment of *E. integriceps* nymphs with PI, hatchability of the laid eggs was reduced [38]. Apart from precocenes, phenolic chromene and hydroxyethyl chromene (isolated from *Ageratum conyzoides*) were found to cause sterility in the bug *Dysdercus flavidus* [155, 156]. Bowers and Aregullin [157] isolated an anti-JH compound, polyacetylenic sulfoxide, from *Chrysanthemum coronarium* which produced sterile adults in *O. fasciatus*. In the present study, all eggs, laid by *S. littoralis* adult females, failed to hatch (zero fertility), regardless the FMev dose or the larval instar under treatment, i.e. FMev caused complete sterilization in the present insect. For explicating the sterility in *S. littoralis* after larval treatment with FMev, some

suggestions can be provided herein. (1) Because FMev caused complete sterility in *S. littoralis*, this compound can be analogous to the allatectomy (surgical removal of corpora allata, JH-producing organs) of last instar larvae of *S. littoralis* which subsequently caused sterility [57, 158]. (2) 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 [159, 160]. These materials are synthesized primarily by fat body during the immature stages [161] or by the ovary *in situ* [162]. Wherever the site of synthesis, FMev might disturb the production of these materials and/or accumulation in adult females of *S. littoralis* leading to sterility. (3) 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 gonadotropic hormone responsible for the regulation of vitellogenin deposition into oocytes [163]. (4) The sterility might 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 [163, 164]. (5) The sterility of *S. littoralis* might 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!!

CONCLUSION

Depending on 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 an anti-JH activity, but JH-like activity, against the present insect. On the other hand, FMev was found a potent anti-gonadotropic compound against *S. littoralis*. However, this compound should be assessed under field conditions before recommendation for use in the IPM program against *S. littoralis*.

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