SECTION-I

JUVENILE HORMONE MIMICS

CHAPTER-I

NATURALLY OCCURRING JUVENILE HORMONE MIMICS

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ABSTRACT

A literature survey of the naturally occurring JH mimics has been carried out. This Chapter gives a summary of published work on JH-mimics found in nature.

NATURALLY OCCURRING JUVENILE HORMONE MIMICS

Insect metamorohosis from juvenile (sexually immature individual) to a reproducing adult is governed essentially by three hormones:

(a) Prothoracotropic or brain hormone produced in the neurosecretory cells of the brain.

(b) Prothoracic or moulting hormone produced in the prothorax.

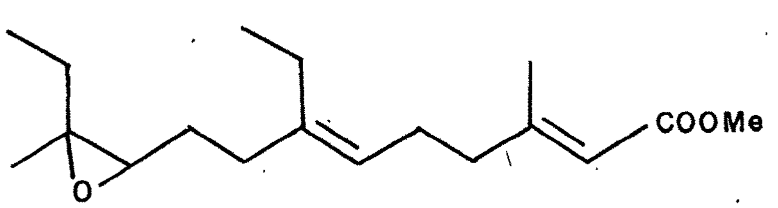
(c) Juvenile hormone.

Juvenile hormone[1] is secreted by two small endocrine glands, the "corpora allata", locatèd behind an insect brain. It serves to maintain the juvenile characteristics of the insect. The corpora allata actually produce the juvenile hormone and then control the amount of hormone which enters the blood stream of insect. The insect will remain sexually immature if a high concentration of the juvenile hormone circulates in the blood stream. This circulation of JH has to stop if the insect is to metamorphose into a mature adult.

In 1956 Williams[2] announced that the abdomen of the male silk moth, <u>Platysamia cecropia</u> L. is an exceptionally rich source of JH and recognised the powerful insecticidal potential of JH. It has been claimed that most mammalian tissues (including human placenta)[3], several microorganisms[4] and the parasite <u>Nosema</u>[5], all showed considerable JH activity.

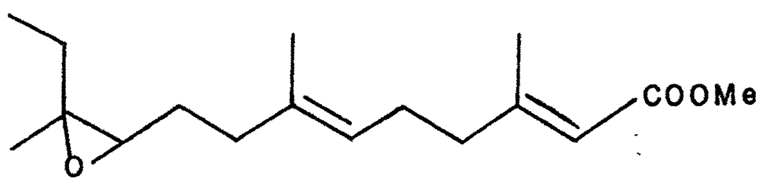
Williams and Law[6], were able to achieve a nearly 50,000 fold concentration of JH activity in the original cecropia extract and established the major component of this material as the 9,10-epoxide of methyl 1-hexadecanoate.

Roller and his co-workers[7] were able to achieve a 10^5-fold purification of the Cecropia extract and thence an elaboration and synthesis led to the gross structure of the hormone. They were able to refine their earlier structural conclusions and deduce that JH is methyl <u>cis</u>-10, 11-epoxy-7-ethyl-3,11-dimethyl-<u>trans</u>-<u>trans</u>-2,6-tridecadienoate, (JH-I)[8], as depicted below.



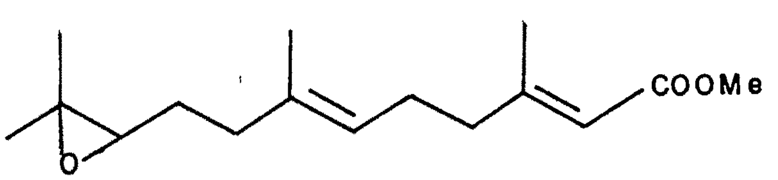
JH – I

Meyer, Schneiderman, Hanzmann and Ko established the presence of JH-II in cecropia oil extracts[9]. They found that the ratio of JH-I: JH-II varied from 4:1 to 10:1. The structure of JH-II was finally established by synthesis[10].



JH – II

Judy et al. also reported the 3rd JH (JH-III)[10g] which is now considered to be the most abundant of the three JHs known so far[10h].

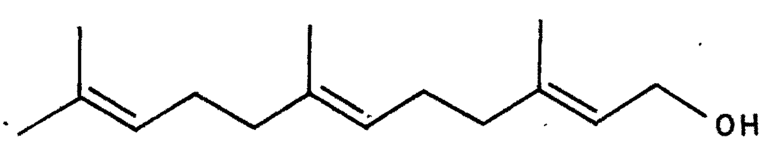


JH – III

The profound effects on the insect when juvenile hormone is present at the wrong time during metamorphosis makes it a key substance in the search for a 'third generation' pesticide. It is convenient to classify the JH-mimics as follows:

a) JH-mimics with acyclic skeleton

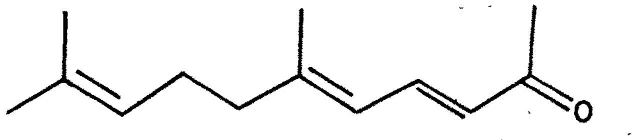
The sesquiterpene alcohol farnesol (1) is undoubtedly one of the first compounds reported to possess juvenile hormone activity. This compound occurs in



(1)

nature in numerous plants and is a supposed intermediate in the biosynthesis of sesquiterpenoids (in the form of farnesyl pyrophosphate). Farnesol is potentially present in all tissues where sesquiterpenoids are formed[11]. So strong was the activity of farnesol that initially it was considered a virtual juvenile hormone[12]. Nevertheless, even after the abandonment of this idea it was demonstrated[12b,13] that juvenile hormone activity of farnesol was evident in many cases especially when applied to *Tenebrio molitor* and *Rhodnius prolixus*.

Pseudoionone (<u>2</u>) obtainable from <u>Nicotiana tabacum</u> when applied topically[14] (62.5 ug) inhibited the development of yellow mealworm <u>T. molitor</u> pupae.



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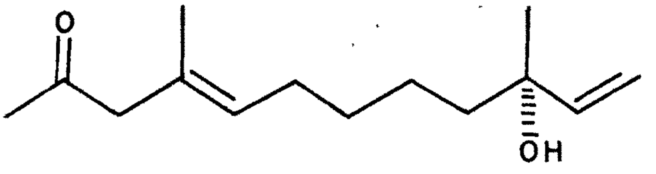

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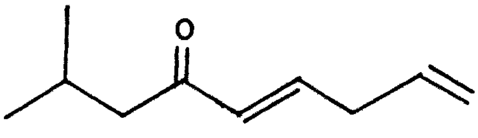
Jacobson <u>et al.</u>[15] isolated Echinolone (<u>3</u>) from American cone flower <u>Echinacea augustifolia</u> roots. It showed strong juvenile hormone activity in <u>T. molitor</u> following its topical application to pupal stage. Its JH rating was 3.0 at 0.97 ug and 2.4 at 0.48 ug (for bio-assay method see Table III).

Saxena <u>et al.</u>[16] have reported the juvenile hormone activity of the steam distilled oil of <u>Tagetes minuta</u>. They observed that topical application of oil to <u>D.koenigii</u> nymphs prevented adult molt but the oil was inactive on the larvae and pupae of the mosquito, <u>Aedes aegypti</u> L. and pupae of house fly, <u>Musca domestica</u>. The active components were not identified though tagetone (4), a known constituent of T. minuta oil, did show JH-mimicking activity on D. koenigii.



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b) JH-mimics with juvabione skeleton

The extraordinary morphogenetic activity of the 'paper factor' proved to be one of the most famous and important developments in search for juvenile hormone mimicking substances from natural sources. Slama and Williams in 1964 observed that Linden bug (P. apterus) larvae which matured normally in Czechoslovakia would not mature when brought to U.S. They narrowed the reason of this mysterious phenomenon to the paper towel used to line the bottoms of vessels containing the larvae. It was found that when the Linden larvae were grown in absence of that paper towel or any paper from northern U.S.A. and Canada, the larvae would develop into normal adult linden bugs. Further research showed that newspapers, magazines and other paper materials manufactured in these geographical areas contain an extractive analogue of JH which selectively attacks only one family of insects - the Pyrrhocoridae (Hemiptera). The JH activity was then found to originate in the balsam fir (Abies balsamea), which is the main source of paper pulp in northern U.S. and Canada. This tree synthesised what was named as "paper factor"[17].

Bowers et al.[18] succeeded in isolating the active ingredient of the 'paper factor' which they found to be a sesquiterpenoid ester with high JH activity for Pyrrhocoris apterus. The ester was identified as the methyl ester of (+)-todomatuic acid (5)[19] (see Chart I) isolated first from bisulfite treated pulp oil of Japanese fir Abies sachalinensis Schmidt and given the name "Juvabion". It had high JH-activity for Choristoneura fumiferana (Spruce budworm), where embryonic development was blocked.[20] The structure was deduced on the basis of spectroscopic considerations.

Cerny et al.[19] isolated from A. balsamea-dubious 10-dehydrojuvabion (6) (besides juvabion) which was slightly more active than juvabion on Pyrrhocoris apterus at 1-3 ug level. It was found to inhibit embryonal development and stop larval growth[21]. These compounds were assigned 6R, 7R stereoconfiguration on the basis of earlier work of Isoe et al.[22]

Manville et al.[23] have shown that the original 'paper factor' effect was not due to juvabion (5) and dehydrojuvabion (6) alone. They isolated and characterised on the basis of spectroscopic and O.R.D. evidence juvabiol (7) and isojuvabiol (8) along with an artefact Δ^{9}-dehydrojuvabi-11-ol (9) from the wood. All of the isolated compounds have 6R, 7R configuration. Their juvenile hormone activity is summerised in Table I.

Pawson et al.[24] synthesised all the four possible diastereoisomers of juvabion and derived their absolute stereochemistry by X-ray analysis. Comparison with juvabion isolated by Cerny et al., they noted that the stereoconfiguration at C_6 and C_7 were R and S respectively.

Pawson et al.[24b] not realising the possibility that there could be two naturally occurring isomers of juvabion and believing that the isolation carried out by Bowers[18] and Cerny[19] came from same species, i.e. A. balsamea felt obliged to correct the original assignment of stereo-configuration from 6R, 7R to 6R, 7S.

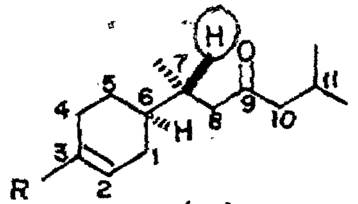
Re-examination of A. balsamea by Manville[25] indicated that juvabion isolated from the tree had 6R, 7R configuration and named 6R, 7S isomer of Cerny[19] as epijuvabion. He further concluded that the tree from which Cerny et al.[19] had isolated 6R, 7S isomer (epijuvabion) was possibly a putative cross and not a true balsam fir. This 'Slovak fir' was named as 'A. balsamea-dubious-dying. Further work on latter[23b] resulted in the isolation of epijuvabion (10), 10-dehydroepijuvabion (11) and epijuvabiol (12). Their juvenile hormone activity is listed in the Table 1.

Abies alba, the widespread European fir and the possible male parent of the 'Slovak fir' was considered the likely genetic source of the 6R, 7S forms of juvabion. Consequently both the juvabion as well as epijuvabion type compounds were reported from this tree by Manville[26]. They reported the occurrance of juvabion (5), 10-dehydrojuvabion (6), juvabiol (7), 10-dehydroepijuvabion (11), isojuvabiol (8) and epijuvabiol (12) thereby confirming Abies alba as possible genetic source of 6R, 7S compounds in the 'Slovak fir'.

Wide variability of occurrence of juvabion analogs was also reported from Abies lasiocarpa[27]. Juvabion (5), juvabiol (7), epijuvabiol (12) and epimeric 8-dehydrojuvabi-7-ols (13) were reported from the whole wood.

Rogers et al.[28,29] isolated (+)-todomatuic acid and (-)-cis-dihydrotodomatuic acid (14) from the wood of Douglas fir, Pseudotsuga menziesii. The structure of dihydrotodomatuic acid (14) was established on the basis of spectroscopic and ORD evidence. Both juvabion and (-)-cis-dihydrotodomatuic acid (14) as methyl ester caused morphogenetic deformity in the pupae of T. molitor. Similar effects were observed on Oncopeltus fasciatus and T. apterus.

Hirose et al.[30] isolated and identified in addition to the above acids pseudotsugonal (15); ar-pseudotsugonal (16); dihydropseudotsugonal (17) and dihydropseudotsugonol (18) from the same tree.



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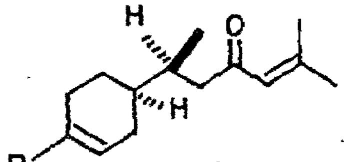

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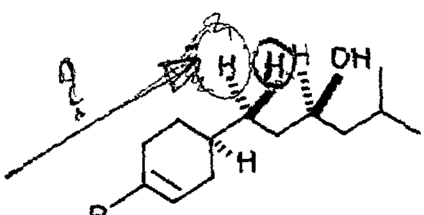

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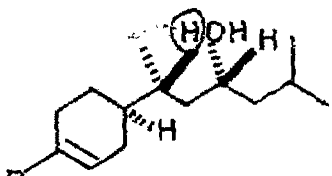

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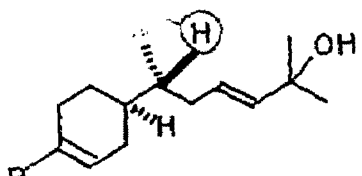

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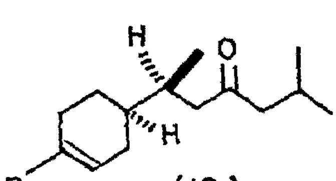

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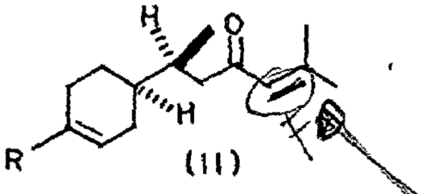

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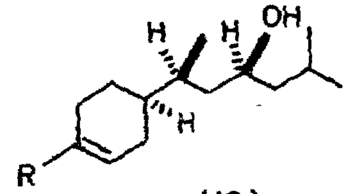

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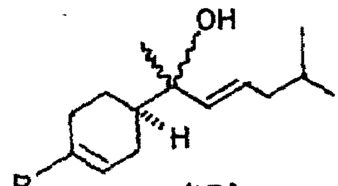

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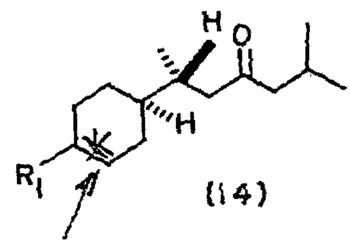

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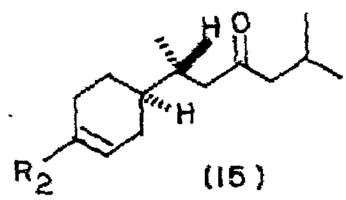

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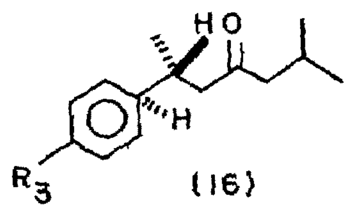

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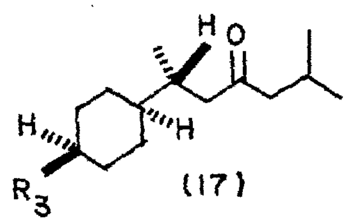

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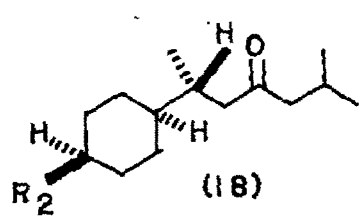

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R = COOMe, R_1 = COOH, R_2 = CH_2OH, R_3 = CHO

Chart I: JH MIMICS WITH JUVABION SKELETON

Table I : JH-MIMICS WITH JUVABION SKELETON

Compound	Structure	Stereo-chemistry	Source
Juvabion	(5)	6R, 7R	A. balsamea, A. alba, A. lasiocarpa P. menziesii
10-Dehydrojuvabion	(6)	6R, 7R	A. alba, A. balsamea(d.d)
Juvabiol	(7)	6R,7R,9S	A. lasiocarpa, A. balsamea, A. alba.
Isojuvabiol	(8)	6R,7R,9R	-do-
Δ^9-Dehydrojuvabi-11-ol	(9)	6R,7R	A. balsamea, A. lasiocarpa
Epijuvabion	(10)	6R, 7S	A. balsamea (d.d)
10-Dehydroepijuvabion	(11)	6R, 7S	A. alba, A. balsamea(d.d)
Epijuvabiol	(12)	6R,7S,9S	A. balsamea (d.d), A. lasiocarpa, A. alba
8-Dehydrojuvabi-7-ols	(13)	6R	A. lasiocarpa
cis-Dihydrotodomatuic acid	(14)	6R,7R	Pseudotsuga menziesii
Pseudotsugonal	(15)	6R, 7R	-do-
ar-Pseudotsugonal	(16)	7R	-do-
cis-Dihydrotsugonal	(17)	6R, 7R	-do-
cis-Dihydrotsugonol	(18)	6R, 7R	-do-

Table II : JUVENILE HORMONE ACTIVITY* OF THE ISOLATED JUVABION TYPE COMPOUNDS ON THE LAST INSTAR LARVAE

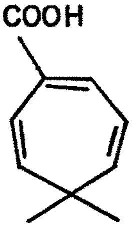
Substance	Pyrrhocoris apterus L.	Dysdercus cingulatus F.	Graphosoma italicum Mull.	Tenebrio molitor L.
		J.H. activity*		
Juvabion	1.7	2.3	in**	in
10-Dehydrojuvabion	5.0	2.0	in	in
Juvabiol	5.0	4.6	in	in
Isojuvabiol & Juvabiol	5.6	4.7	in	in
Δ^9-Dehydrojuvabiol	2.1	2.1	in	in
Epijuvabion	4.5	4.3	in	in
10-Dehydroepijuvabion	7.0	4.0	in	in
Epijuvabiol	30.0	12.0	in	in

* The values indicate amount of the compound in micrograms which cause in topical application just 50% retention of juvenile morphological characteristics (10-50 morph units).

** in: inactive upto 500 ug per speciman in topical application.

c) Miscellaneous type

(i) Plant acids: Thujic acid (19) isolated from the heartwood of Western red cedar *Thuja plictata* Donn ex. D. Don, showed significant juvenile hormone activity after injection



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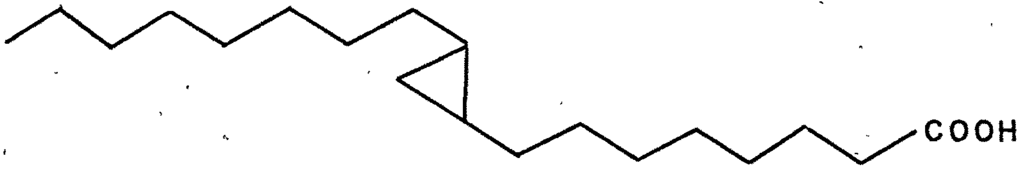
into pupae of the yellow mealworm, *T. molitor* L.[31]

Sterculic acid (20) isolated from the oil of *Sterculia foetida* L. seeds, greatly affected the life cycle



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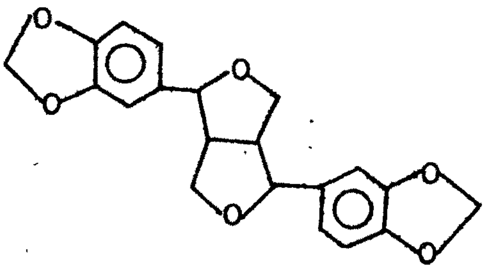
of blow fly, *Phaenicia (Lucilia) sericata* (Meigen) when fed to the larvae[32].

(ii) Lignans: Low juvenile hormone activity of natural components of Sesame (Sesamum indicum) oil- Sesamine (21)



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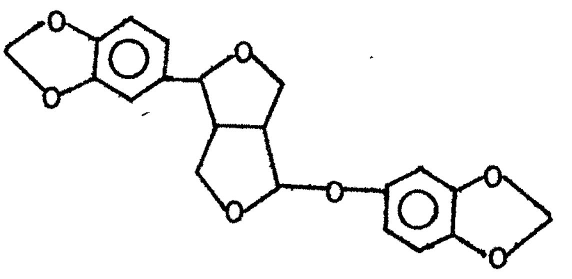

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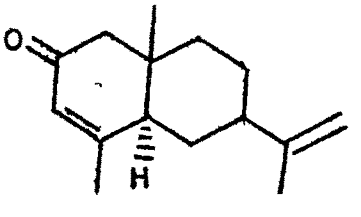
and Sesamoline (22) was found in the case of the mealworm T. molitor and the milkweed bug, Oncopeltus fasciatus[33].

(iii) Enones: Nootkatone (23) and some of its derivatives viz. epoxy nootkatone occurring in the essential oil of



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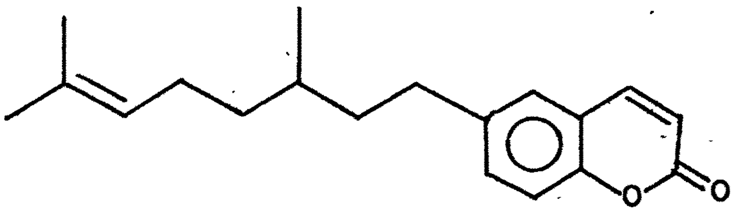
orange, Citrus lemon were found to exhibit weak juvenile hormone activity on the pupae of Triboleum castaneum.[34]

Ostruthin (24), the naturally occurring coumarin of



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the roots of Imperatoria ostroruthium was shown to have weak juvenile hormone activity.[33]

(iv) Plant extracts: Nymphs of Dysdercus koenigii F. when treated with dorsal applications of acetone extract of roots of Iris ensata either failed to reach adulthood or molted into adults with crippled wings.[35]

Juvenile hormone activity was also investigated in some twelve south Indian plants[36]. All of them contained different degrees of juvenomimetic activity. Experiments using Morus alba extract showed the presence of a juvenile hormone analog in the plant.[36]

High juvenile hormone activity is exhibited by the extracts of Vetiveria zizanioides (Vettiver); Ocimum *basilicum* (Pachilai); *Pelargonium graveolans* (Geranium); *Bauhinia purpurea*; *Polypodium vulgare*; *Polyscias guiefoylee*; *Nephrolepsis exaltata*; *Parthenium pysterophorus* (carrot weed); and *Catharanthus roseus* (Nithya Kalyani)[37].

Extract of *Organum vulgare* also exhibits high juvenile hormone activity on *D. koenigii*[38].

Ether extract of *Attacus atlas* L.[39] contained an active substance which had similar chromatographic behaviour as JH-II. Soyabean meal extract too had JH activity.[40]

Jacobson *et al.*[41] surveyed a number of plants for juvenile hormone activity. The plants which showed distinct JH activity are summerised in Table III.

It can be expected that the present relatively high activity in the area of search for newer and more active JH-mimics from natural plant sources as well as in the area of synthesis of JH-analogs might result in the discovery of new JH-mimics that will have broad spectrum of activity towards a wide range of harmful insects, thus bringing far-reaching changes in the practice of biological control of insects.

Table III : PLANTS WHOSE ETHYL ETHER EXTRACT SHOWED JH ACTIVITY* IN TENEBRIO OR Oncopeltus fasciatus

Plant family	Botanical name	plant part**	JH rating	
			T.molitor	O.fasciatus
Clethraceae	Clethra alnifolia	st-lf-fl-fr	0.0	3.0
Iridaceae	Iris douglasiana	rh-rt-st-fr	0.2	2.0
Lauraceae	Sassafras albidum	wr-rb	1.0	3.0
Myrtaceae	Eucalptus camaldulensis	ws-sb	0.0	2.0
Pinaceae	Chamaecyparis lawsoniana	sd	2.2	0.0
	Pinus rigida	tw-lf	0.2	1.6
	Tsuga canadensis	lf	0.0	1.0
Celastraceae	Maytenus senegalensis	ws-sb	-	a+

* Method of bio-assay: 500 ug of extract (in 1 ul of acetone) was applied topically to the venter of the last three abdominal segments of each newly molted pupa. All pupae or nymphs were held until the following molt to determine JH activity which was signalled by the presence of immature characters. In Tenebrio, activity was rated as 0 = perfect adult; 1,2, = retention of gin traps or urogompi; 3 = same as 1,2 plus retention of pupal cuticle at the area of treatment; 4 = 2nd pupa with all pupal characters. In Oncopeltus rating was 0 = perfect adult; 1 = retention of nymphal coloration in abdomen; 2 = adult with reduced wings and nymphal coloration; 3 = supernumerary nymph. The average rating was calculated by multiplying the number of pupae or nymphs by their numerical activity ratings and dividing the sum by number of insects tested.

** fl: flower; st: stem; lf: leaf; fr: fruit; rh: rhizome; rt: root; wr: wood of roots (bark removed); rb: root bark; ws: wood of stem (bark removed); sb: stem bark; sd: seed; tw: twig.

+ a: At 62.5 ug a JH rating of 2.0 was obtained.

R E F E R E N C E S

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