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Chapter 48

Diterpenoids as Insect Antifeedants and Growth Inhibitors: Role in *Solidago* Species

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Diterpenoids have a wide range of biological activities. Their role in plant-insect interactions, both as antifeedants and growth inhibitors, is reviewed. Four ent-kauranes, kaur-16-en-19-oic acid, (-)-kauran-16α-ol, 15α-hydroxy-(-)-kaur-16-en-19-oic acid, and 17-hydroxy-(-)-kaur-15-en-19-oic acid, have recently been isolated from the leaves of Solidago nemoralis. These compounds were found to have antifeedant activity against Trirhabda canadensis.

Plant chemists show several different approaches to the way they view chemicals in plants. Some are interested in the isolation of the molecule per se, its structure and synthesis (1). Others are searching for interesting and hopefully patentable biologically active plant products or molecules as new drugs (2), as antibiotics (3), or as pesticides (4). A third group seeks to understand the role such compounds (allelochemicals) play in the environment, that is the way in which they may influence or control many of the complex interactions that occur between living organisms in natural plant communities (5, 6). As has been shown in this Symposium these three approaches are not necessarily mutually exclusive.

A study of the latter type is made more difficult since plants, even a single plant, usually contain a large number of different classes of chemical compounds and at the same time may be interacting with a wide variety of different organisms as well as with each other (7, 8). Nevertheless over recent years great progress has been made towards understanding the role of allelochemicals in natural systems particularly with regard to insect-plant interactions (9-12).

Terpenoids are one of the many classes of allelochemicals known to play an important role in such interactions (13). Of particular interest are the diterpenoids. These are widely distributed in plants and are also present in fungi and marine organisms, and as such provide a ready source for the isolation of new compounds (13-15). They also show a wide range of biological activities (13-15). These include antitumor properties (16), antimicrobial activity (17),

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fertility regulation (18), plant growth regulation (19, 20), and allelopathic action (21). Several groups of diterpenoids are also known to be active as larval growth inhibitors or feeding deterrents against a number of agricultural and forest pests (22-24) (Table I).

Biological Activity of Diterpenes Against Insects

Bicyclic diterpenes-clerodanes. An important group of insect antifeedants are the clerodane diterpenoids, which have been isolated from several different plant families (13) (Figure 1). Particularly well studied are the antifeedant activities of caryoptin and clerodin, and their derivatives, from *Clerodendron* and *Caryopteris*, Verbenaceae, against the tobacco cutworm *Spodoptera litura* L. (25-27).

Examining the bitter-tasting leaves of *Ajuga remota*, an East African medicinal plant, known locally to be resistant to insects, led to the isolation of another group of clerodanes, the ajugarins, active against both the monophagous African armyworm, *Spodoptera exempta*, and the polyphagous *S. littoralis* (22, 28). When added to artificial diets ajugarins are also insecticidal to the silkworm, *Bombyx mori*, but merely inhibit the growth of the pink bollworm, *Pectinophora gossypiella* (28). Ajugareptansones A and B from *A. reptans* (29, 30), and ivains I-IV from *Ajuga iva* also exhibit high antifeedant activity against the African armyworm and other lepidopterous species (31).

Two chlorine-containing clerodanes, tafricanins A and B, with similar antifeedant properties, have been isolated from a South African bush, *Teucrium africanum* (32). Teucjaponin B, from *Teucrium japonicum*, is also inhibitory to the feeding of *Spodoptera litura* (33).

Belles *et al.* have recently discussed the structure-activity relationships of several natural clerodane diterpenoids and their derivatives, and have compared their activity with that of some synthetic butenolide derivatives (34).

Grindelane diterpenoids. Grindelanes, labdane-type diterpenoids (Figure 2) from *Chrysothamnus* and *Grindelia* species, show significant antifeedant activity (35). Two grindelane diterpenes, 18-hydroxygrindelic acid and 18-succinyloxygrindelic acid, present in the bicarbonate-soluble fraction of *Chrysothamnus nauseosus* (Pall.)Britt, the rabbit bush, were found by Rose (36) to inhibit feeding of third-instar Colorado potato beetles. Additional grindelane diterpenes, 6α-hydroxy and 6β-hydroxygrindelic acids, also inhibited feeding by the aphid *Schizaphis graminum* (37).

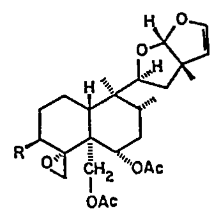
Cuticular diterpenes-duvanes and labdanes. Cutler *et al.* have found that the cuticular diterpenes of green tobacco have both allelopathic and insect-deterrent effects (38). Present in the cuticle are duvane and/or labdane diterpenes (Figure 3). The levels of these specific cuticular components are believed to be responsible for the observed resistance of some types of tobacco to green peach aphids *Myzus persicae* (Sulzer), tobacco budworm *Heliothis virescens* (F.), and tobacco hornworm *Manduca sexta* (L.) (39).

Tricyclic diterpenes-resin acids. Wood resin constituents, e.g. abietane derivatives, have also been implicated in pest resistance (Figure 4). Among the conifer-associated sawflies many prefer to feed

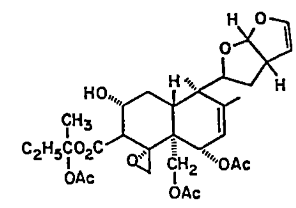
Table I. Diterpenes with Known Biological Activity against Insects

Source	Family	Diterpene(s)	Insect affected	Reference
Clerodanes				
Clerodendron tricotomum	Verbenaceae	Clerodendrins A & B, 3-epicaryoptin	*Spodoptera litura*	(25-27)
C. cryptophyllum	Verbenaceae	Clerodendrin A	*Spodoptera litura*	(25-27)
Caryopteris divaricata	Verbenaceae	Caryoptin, clerodin, and derivatives	*Spodoptera litura*	(25-27)
Ajuga remota	Labiatae	Ajugarins I-IV	*Spodoptera littoralis*, *Spodoptera exempta*, *Schistocerca gregaria*, *Bombyx mori*, *Pectinophora gossypiella*	(22, 28)
A. reptans	Labiatae	Ajugareptansones A & B	*Spodoptera littoralis*	(29, 30)
A. iva	Labiatae	Ivains I-IV	*Spodoptera littoralis*	(31)
Teucrium africanum	Labiatae	Tafricanins A & B	*Locusta migratoria*	(32)
T. japonicum	Labiatae	Teucjaponin B	*Spodoptera litura*	(33)
Grindelane diterpenoids				
Chrysothamnus nauseosus	Asteraceae	18-Hydroxygrindelic and 18-succinyloxygrindelic acids	*Leptinotarsa decemlineata*	(36)
		6α-Hydroxygrindelic and 6β-hydroxygrindelic acids	*Schizaphis graminum*	(37)
Duvanes and labdanes				
Nicotiana spp.	Labiatae	Labda-12,14-dien-8α-ol, labda-13-en-8α,15-diol, α&β-4,8,13-duvatrien-1,3-diols, α&β-4,8,13-duvatrien-1-ols	*Heliothis virescens*, *Manduca sexta*, *Myzus persicae*	(39)
Abietanes				
Pinus banksiana	Pinaceae	13-oxo-8(14)-podocarpen-18-oic, dehydroabietic,	*Neodiprion swainei*, *N. rugifrons*, *N.*	(40-42)

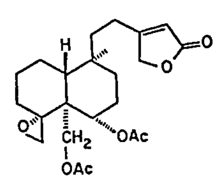
		palustric, levopimaric, neoabietic acids	dubiosus, N. lecontei	
Larix laricina	Pinaceae	Abietic, neoabietic, dehydroabietic, isopimaric, sandaracopimaric acids	Pristiphora erichsonii Schizaphis graminum	(43, 44) (37)
Norditerpenedilactones				
Podocarpus nivalis, P. hallii, P. gracilior	Podocarpaceae	Nagilactone C, D, F, podolide	Pectinophora gossypiella, Heliothis zea, Spodoptera frugiperda, Musca domestica, Laspeyresia pomonella, Epiphyas postvittana	(45-47)
Grayanoid diterpenes				
Kalmia latifolia	Ericaceae	Kalmitoxin-I, kalmitoxin-IV, grayanotoxin-III	Lymantria dispar	(48)
Kauranes				
Helianthus annuus	Asteraceae	Trachyloban-19-oic and kaur-16-en-19-oic acids	Homoesoma electellum, Heliothis virescens, H. zea, Pectinophora gossypiella	(50, 51)
Helianthus spp.	Asteraceae	Ciliaric and angelylgrandifloric acids	Homoesoma electellum	(52)
H. occidentalis	Asteraceae	(-)-cis and (-)-trans ozic acids	Lepidopterous larvae	(54)
Isodon diterpenes				
Rhabdosia spp.	Labiatae	Isodons and derivatives	Spodoptera exempta, S. littoralis	(55, 56)



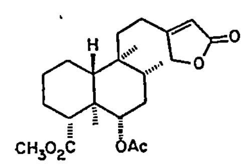
R = OAc: 3-epicaryoptin
R = H: clerodin



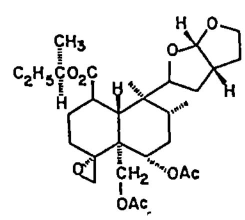
clerodendrin A



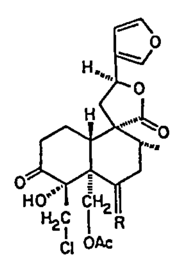
ajugarin I



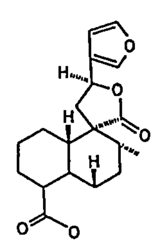
ajugarin IV



ajugareptansin

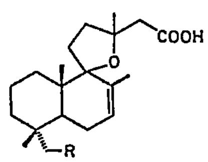


R = O: tafricanin A
R = α-OAc, β-H: tafricanin B

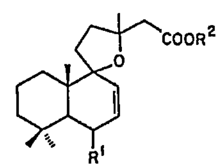


teucjaponin B

Figure 1. Clerodanes with insect antifeedant activity.

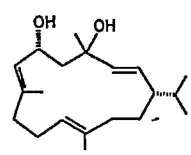


R = OH: 18-hydroxygrindelic acid
R = $OCOCH_2CH_2COOH$: 18-succinoyloxygrindelic acid

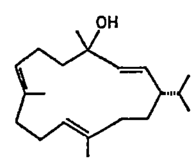


R^1 = α-OH, R^2 = H: 6α-hydroxygrindelic acid
R^1 = β-OH, R^2 = H: 6β-hydroxygrindelic acid

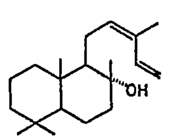
Figure 2. Grindelanes with insect antifeedant activity.



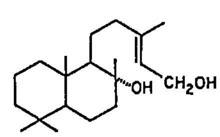
α & β-4,8,13-duvatrien-1,3-diols



α & β-4,8,13-duvatrien-1-ols



Labda-12,14-dien-8α-ol



Labda-13en-8α,15-diol

Figure 3. Cuticular Diterpenoids--Duvanes and Labdanes important in host-plant resistance to insects.

on mature needles rather than on the current season's needles of their respective hosts. Bioassay studies with needle extracts indicate that diterpene resin acids are important repellents.

All and Benjamin (40) observed that the monophagous sawfly species, Neodiprion swainei Midd. and N. rugifrons Midd., did not feed on juvenile foliage of their host jackpine, Pinus banksiana Lamb. The antifeedants were found by Ikeda et al. (41) to be 13-oxo-8(14)-podocarpen-18-oic acid and dehydroabietic acid. Schuh and Benjamin, working with two additional species of sawfly, N. dubiosus and N. lecontei (Fitch), found that palustric and levopimaric acids and neoabietic and palustric acids respectively, when painted on to one-year-old foliage of jackpine, also acted as feeding deterrents (42).

Diterpene resin acids, abietic, dehydroabietic, 12-methoxyabietic, sandaracopimaric, and isopimaric, are also antifeedants for the larch sawfly, Pristiphora erichsonii (Hartig) (43). Abietic, neoabietic, dehydroabietic, and isopimaric acids significantly reduce consumption rates, feeding efficiences, and growth rates when topically applied to their natural food plant, tamarack, Larix laricina (Du Roi) K.Koch (44). Pure sandaracopimaric acid and levopimaric acid also act as feeding deterrents to aphids (37).

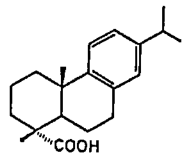
Norditerpenedilactones. The resistance of Podocarpus nivalis and P. hallii to insect attack is attributed to the high concentration of the norditerpenedilactone, nagilactone C, in the foliage (45, 46). Podocarpus gracilior is also resistant in nature to insect attack. As part of an apparently multichemical defense mechanism, nagilactones C, D, F and podolide (Figure 5) show insecticidal activity against Heliothis zea, Spodoptera frugiperda, and Pectinophora gossypiella (47).

Grayanoid diterpenes. A number of grayanoid diterpenes have been isolated from the mountain laurel, Kalmia latifolia L. (Figure 6) (Ericaceae). Kalmitoxin-I is the major antifeedant to the polyphagous gypsy moth, Lymantria dispar (48). Kalmitoxin-IV and grayanotoxin-III are also significantly deterrent to feeding.

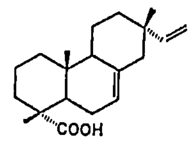
Tetracyclic diterpenes-kauranes. Several diterpene carboxylic acids from Helianthus species have been shown to inhibit insect growth (49) (Figure 7). Kauranes, trachyloban-19-oic and ent-kaur-16-en-19-oic acids, found in the florets of Helianthus annuus, inhibit larval development of the sunflower moth, Homeosoma electellum L. (50), and of several other lepidopterous species (51). These acids are widely distributed in other Helianthus species and may be important in the resistance of sunflowers to insects. Herz et al.(52) have recently shown that two other kauranes from the sunflower, ciliaric acid and angelylgrandifloric acid, when fed to the sunflower moth result in both higher mortality and retardation of growth. However ciliaric acid, from H. argophyllus, shows no insecticidal activity against Spodoptera litura or Culex pipiens (53).

Two diterpenoid acids, (-)-cis- and (-)-trans-ozic acids, may also contribute to host plant resistance to several insect species in Helianthus occidentalis (54).

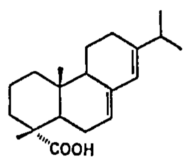
Isodon diterpenes. Highly oxygenated 6-seco-ent-kaurane diterpenoids, the isodons (Figure 7), isolated from species of Isodon (now Rhabdosia)



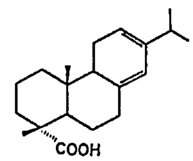
dehydroabietic



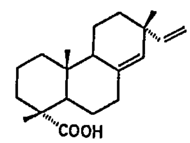
isopimaric



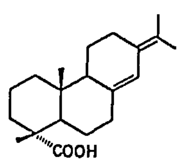
abietic



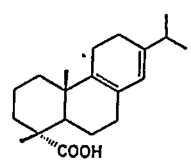
levopimaric



sandaracopimaric

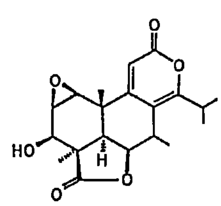


neoabietic

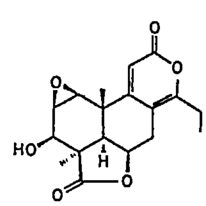


palustric

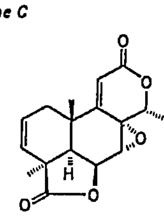
Figure 4. Abietanes with insect antifeedant activity.



nagilactone C

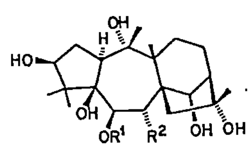


nagilactone D

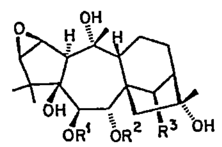


podolide

Figure 5. Norditerpenedilactones with insect antifeedant activity.

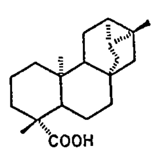


$R^1 = H$, $R^2 = OH$: *kalmitoxin-I*
$R^1 = R^2 = H$: *grayanotoxin-III*

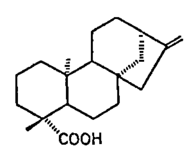


$R^1 = Ac$, $R^2 = H$, $R^3 = OH$:
kalmitoxin-IV

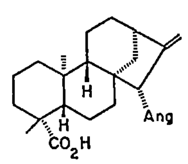
Figure 6. Grayanoid Diterpenes with insect antifeedant activity.



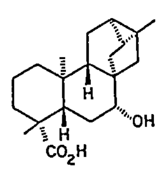
trachyloban-19-oic acid



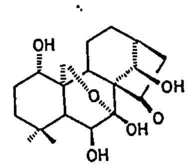
kaur-16-en-19-oic acid



angeloylgrandifloric acid



ciliaric acid



isodonol

Figure 7. Kauranes that inhibit insect growth and development.

show growth inhibitory activity against both Spodoptera exempta and S. littoralis (55, 56). The growth inhibitory activities appear to be relatively specific for lepidopterous larvae.

The Genus Solidago

Solidago is a mostly North American genus of about 125 species. It belongs to the Asteraceae (Compositae), a family with a very distinctive chemistry (57, 58). The genus itself contains several different classes of secondary compounds including a number of diterpenes (59). During the 1960's and 1970's Anthonsen in Finland, and McCrindle and his coworkers in Canada, isolated about twenty-five different compounds from the roots of Solidago species, mainly clerodanes and labdanes. But in the last five years attention has turned to the aerial parts of the plant and compounds of several other classes of diterpenes, abietanes and kauranes, have been isolated (60-79) (Table II).

As many of the same types of diterpenes play an active role in the resistance of other plants to insect attack (see above), it is interesting to investigate the role of diterpenes in Solidago and its interactions with insects. Solidago has the advantage that the behavior and the ecology of many of the associated insects are well known (80).

Solidago is subject to colonization by a number of different phytophagous insects (81-87), parasites, and predators (88-90). Many of these insects are highly selective in their choice of food plants (91-93), as are, for example, Trirhabda beetles (Coleoptera, Chrysomelidae), which will feed on certain interspersed species of goldenrods but will avoid others. T. canadensis readily feeds on the leaves of both S. altissima and S. missouriensis but completely rejects either S. nemoralis or S. rigida when all four species are growing in the same garden (92). Messina also found that T. virgata rejected S. nemoralis to a greater extent than other Solidago species under field conditions (93). Thus S. nemoralis appears to be particularly well defended against Trirhabda beetles, (92, 93), suggesting a possible role for the diterpenes in S. nemoralis as feeding deterrents.

Isolation of Diterpenes from Solidago Species

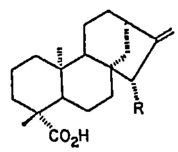
Leaves of S. nemoralis and S. altissima were collected from Professor P. Morrow's experimental gardens located at Cedar Creek, University of Minnesota.

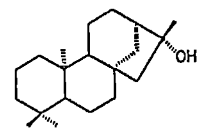
Dry milled plant material was thoroughly extracted with petroleum ether/ether (2:1) (67). The extracts were separated on a kieselgel 60 silica column, and eluted with petroleum ether/ethyl acetate and ethyl acetate/methanol mixtures of increasing polarity. Compounds were further purified by silica TLC using a variety of solvents or on a HPLC, Dynamax semipreparative silica column, with 98% hexane/2% dichloromethane solvent.

Four kauranes present in the petroleum ether/ethyl acetate fractions of S. nemoralis were fully characterized by mass spectrometry, nuclear magnetic resonance spectrometry and infrared as (-)-kaur-16-en-19-oic acid, (-)-kauran-16α-ol, 15α-hydroxy-(-)-kaur-16-en-19-oic acid and 17-hydroxy-(-)-kaur-15-en-19-oic acid

Table II. Distribution of Diterpenes in Species of Solidago

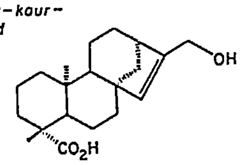
Species	Plant part	Class	References
Solidago altissima L.	Roots	Clerodanes	(60)
	Leaves	Clerodanes	(61, 62, 63)
S. arguta Ait.	Roots	Clerodanes	(64)
S. canadensis L.	Roots	Labdanes	(65, 66, 67)
	Leaves	Labdanes	(67)
S. elongata Nutt.	Roots	Clerodanes	(68)
S. flexicaulis L.	Roots	Absent	(69)
S. gigantea Ait. var. serotina Cronq.	Roots	Clerodanes	(70, 71, 72)
S. juncea Ait.	Roots	Abietanes, clerodanes, ent- kauranes	(72)
S. missouriensis Nutt.	Roots	Abietanes, labdanes	(73, 74)
	Leaves	Kauranes	(75)
S. nemoralis L.	Roots	Clerodanes	(67)
	Leaves	Abietanes	(67)
S. odora Ait.	Roots	Absent	(67)
	Leaves	Absent	(67)
S. rigida L.	Roots	Kauranes	(69)
	Leaves	Kauranes	(75)
S. rugosa Mill.	Roots	Abietanes, clerodanes, kauranes, labdanes	(67)
	Leaves	Kauranes, labdanes	(67)
S. sempervirens L.	Leaves	Labdanes	(76)
S. serotina Ait.	Roots	Clerodanes	(77, 78)
S. shortii Torr. & Gray	Roots	Clerodanes	(69)
S. virgaurea L.	Roots	None	(69)
	Leaves	Clerodanes	(79)





R = H: kaur-16-en-19-oic acid
R = OH: 15α-hydroxy-(−)-kaur-16-en-19-oic acid

(−)-kauran-16-ol



(−)-17-hydroxy-kaur-15-en-19-oic acid

Figure 8. Kauranes isolated from the leaves of *Solidago nemoralis*.

Table III. Effect of Diterpenes from *Solidago nemoralis* on Feeding by Larvae and Adults of *Trirhabda canadensis*

Compound	Feeding Inhibition (%)[a]	
	Larvae	Adults
Kaur-16-en-19-oic acid	no significant effect	stimulatory**[b]
ent-Kauran-16α-ol	40**	33**
15α-Hydroxy-(−)-kaur-16-en-19-oic acid	42**	49***
17-Hydroxy-(−)-kaur-15-en-19-oic acid	42**	49**
In combination	42*	32*

a) Concentration 1 mg/mL. Results from 20 replicates of three separate experiments
b) Significance levels (Paired T-test)
* 0.05 ** 0.01 *** 0.001

(Figure 8) (94). These four compounds were not present in S. altissima.

Antifeedant activity of kauranes isolated from S. nemoralis

A modification of the disc assay method was used to test the isolated kauranes for antifeedant activity. Freshly collected leaves of S. altissima were painted with the pure compound, dissolved in methanol, at concentrations of 1 mg/mL and 0.5 mg/mL in order to approximate the concentration present in the leaves. Control leaves were coated with methanol. Two treated and two untreated leaves were placed in a petri dish containing moistened filter paper. Eight Trirhabda larvae or four adults, collected from the same field site, were starved for several hours, introduced into the dishes and these kept under standard conditions for a period of twenty-four hours. Feeding was determined in two ways : by visually estimating the total amount of damage to each leaf and by weighing the leaves before and after the experiment. There was no significant difference between the results obtained using either of these methods. Antifeedant activity is expressed as the ratio consumed area of treated leaf/ consumed area of control.

Most previous experiments with kauranes and closely related compounds have been concerned with their effects on insect growth and development. However in this case the deterrent effects of the isolated compounds to Trirhabda canadensis were investigated as a first step in understanding the feeding behavior of this insect in the field.

(-)-Kaur-16-en-19-oic acid had no deterrent effect on feeding by larvae of Trirhabda , but surprisingly was stimulatory to feeding by the adults (Table III). The three other kauranes significantly reduced feeding, in the larvae by 40 per cent and by 32-49 per cent in the adults. In combination the four compounds reduced feeding by 32 per cent. Overall this constitutes a substantial reduction in feeding by Trirhabda beetles and confirms the allelopathic role ascribed to diterpenes.

However these compounds either singly or in combination do not account for the total lack of feeding activity observed either in the laboratory or in the field. Resistance of S. nemoralis to insect attack seems to involve, as is expected, not a single class of compounds but a multichemical response. Other compounds isolated from S. nemoralis showing antifeedant activity to Trirhabda canadensis are at present under investigation.

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