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REVIEW

BIOLOGICAL ACTIVITIES OF SESQUITERPENE LACTONES

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Key Word Index—Compositae; liverworts; sesquiterpene lactones; biological activities; mechanism of action.

Abstract—Sesquiterpene lactones are characteristic constituents of the Compositae but also occur sporadically in other angiosperm families and even in some liverworts. These bitter substances often contain as a major structural feature an α,β-unsaturated-γ-lactone, which in recent studies has been shown to be associated with anti-tumor, cytotoxic, anti-microbial and phytotoxic activity. They are known to poison livestock, to act as insect feeding deterrents and to cause allergic contact dermatitis in humans. This review highlights the present state of knowledge on the biological activities and mechanism of action of some sesquiterpene lactones.

INTRODUCTION

During the past 20 yrs over 500 sesquiterpene lactones have been isolated and identified from many species of higher and lower plants, chiefly from species of Compositae. Although numerous reviews have been concerned with the chemistry, biogenesis, distribution, and chemotaxonomy of sesquiterpene lactones [1–9, 19], an up-to-date review on their biological activity is so far lacking. We have undertaken to assemble what is known about these lactones in terms of their physiological and pathological activities in numerous biological systems, and to comment on their distribution and possible mechanism of action.

Definition, biogenesis and general distribution of sesquiterpene lactones

Sesquiterpene lactones are colorless, bitter, relatively stable, lypophilic constituents which are biogenetically derived from *trans,trans* farnesyl pyrophosphate [6] following an initial cyclisation and subsequent oxidative modifications [3, 7]. The major types of lactones resulting from these enzyme-mediated cyclisations are classified primarily on the basis of their carbocyclic skeletons as; germacranolides, guaianolides, pseudoguaianolides, eudesmanolides, eremophilanolides, and xanthanolides (Fig. 1 presents skeletal types). The suffix "olide" refers to the lactone group [10]. The α,β-unsaturated lactone is either *cis*- or *trans*-fused to the C_6–C_7 or C_8–C_7 positions of the carbocyclic skeleton. Structural modifications of the basic terpene skeleton involve the incorporation of an epoxide ring, hydroxyl groups (generally esterified), and/or a 5-carbon acid, such as tiglic or angelic acid [1]. Some sesquiterpene lactones also contain covalently bound halogen atoms [11].

An individual plant species generally yields only one skeletal type, with oxidative variations on that skeleton. In genera having wide-ranging geographical distributions, a given species may exhibit considerable infraspecific variation in its sesquiterpene lactone structures [12]. For example, the weedy annual, *Ambrosia confertiflora* elaborates as many as four different sesquiterpene lactone-types in populations derived from Mexico and central Texas [13]. The highest concentration of lactones is found in the leaves and flowering heads (phyllaries). Large amounts are stored in glandular trichomes of the upper leaf surface, phyllaries and achenes of *Parthenium hysterophorus* [14]. Other species of the Compositae which are known to contain lactones also elaborate similar glandular hairs, but the chemical constituents of the hairs have not been investigated (Rodriguez, E., unpublished observations). The percentage of lactones obtained can vary quantitatively in a given species from 0.001–5% dry wt. In taxa of *Artemisia*, the lactone content may vary from winter to summer [15]. Lactones are rarely found in stems and roots but eudesmanolides have been reported from the roots of *Liriodendron tulipifera* (Magnoliaceae) [16] and from the bark of numerous Brazilian species of *Eremanthus* (Compositae) [18].

Sesquiterpene lactones are common constituents of most genera of the Compositae (Table 1), with the exception of the evolutionary "advanced" tribe, the Tageteae [13]. They have been reported to occur sporadically in genera of the Umbelliferae, Magnoliaceae, Lauraceae, Winteraceae, Illiciaceae, Aristolochiaceae, Menispermaceae, Cortiariaceae and Acanthaceae [1]. Eudesmanolides, similar to those found in the genus *Inula* (Compositae), are also present in the liverworts (Hepaticae), *Frullania dilatata*, *F. tamarisci* [20] and *Diplophylum albicans* [21].

BIOLOGICAL ACTIVITY OF SESQUITERPENE LACTONES

Anti-tumor and cytotoxic activity. Plant extracts that exhibit actineoplastic (anti-cancer) activity have received considerable attention particularly in the last

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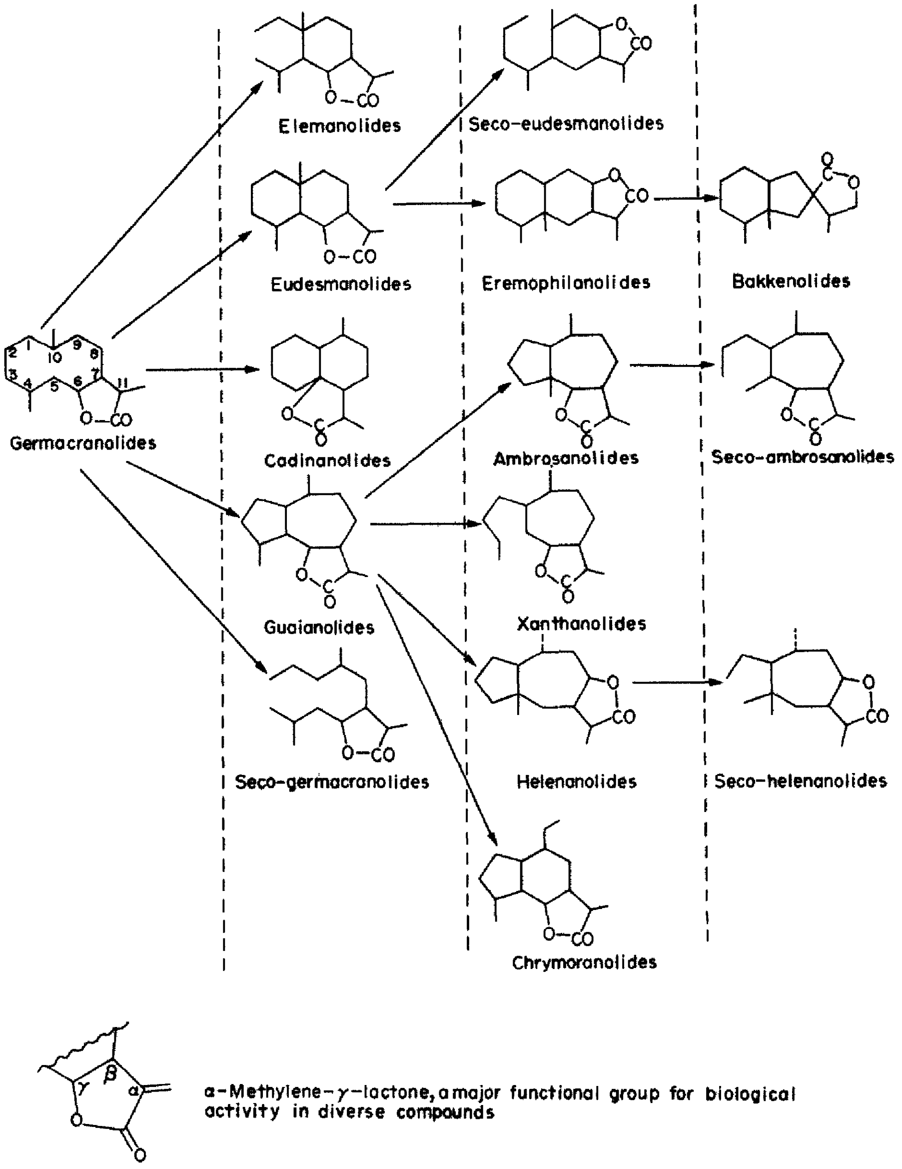


Fig. 1.

decade [17, 22–35]. In a review (1969) of actineoplastic agents from plants, over 50 sesquiterpenes were evaluated for their growth-inhibitory potential against numerous tumor models [22]. It was found that all the known cytotoxic sesquiterpenes contained a lactone function; all but one of these was α,β-unsaturated and the α-ethylenic linkage was exocyclic in every case. In a further study of the structure–activity relationship among sesquiterpene lactones [23] it was noted that the presence of a C_{11}–C_{13} exocyclic double bond conjugated to the γ-lactone was essential for cytotoxicity. Compounds having endocyclic double bonds gave unstable cysteine adducts and were inactive. However, sesquiterpene lactones which incorporated a cyclopentenone, or α-methylene lactone (in addition to the α,β-methylene-γ-lactone) appeared to produce enhanced cytotoxicity. None of the monofunctional sesquiterpenes containing only an α,β-unsaturated ester or cyclopentenone displayed significant activity [23, 26, 27].

In a recent study of bakkenolides from *Petasites albus*, *P. fragrans* and *P. hybridus* [29] it was noted that bakkenolide-A (Fig. 2) a β-methylene-α-lactone (which does not have an $O{=}C{-}C{=}CH_2$ system) gave results against cells derived from human carcinoma (H. Ep-2, Table 2) similar to that reported for other sesquiterpene lactones [28]. This recent finding suggests that other structural parameters must be taken into consideration when evaluating the cytotoxic potential of sesquiterpene lactones and absolute purity of test samples is obviously a prerequisite for precise study.

Table 2 includes those sesquiterpene lactones that exhibit antitumor activity. As noted by numerous workers [26, 28], the structures and reactivities of these sesquiterpene lactones (Fig. 2) may be associated with

Table 1. Distribution of different structural classes of sesquiterpene lactones in the Compositae (modified from Mabry and Bohlmann, 1976)

Tribes (No. Genera)	No. genera with sesquiterpene lactones	Type of lactones present*
Eupatorieae (50)	4	Germacranolides, Elemanolides, Guaianolides, Ambrosanolides, Seco-Ambrosanolides
Vernonieae (50)	4	Germacranolides, Elemanolides, Guaianolides
Astereae (100)	1	Guaianolides
Inuleae (300)	5	Germacranolides, Elemanolides, Guaianolides, Xanthanolides, Ambrosanolides, Helenanolides, Seco-Eudesmanolides, Seco-Ambrosanolides
Heliantheae (including subtribe Ambrosiinae) (250)	24	Germacranolides, Elemanolides, Guaianolides, Eudesmanolides, Xanthanolides, Ambrosanolides, Helenanolides, Seco-Eudesmanolides, Seco-Ambrosanolides, Seco-Helenanolides
Helenieae (60)	11	Germacranolides, Elemanolides, Guaianolides, Eudesmanolides, Helenanolides, Seco-Eudesmanolides, Seco-Helenanolides
Tageteae (15)	0	None
Senecioneae (50)	4	Germacranolides, Xanthanolides, Eremophilanolides, Helenanolides, Bakkenolides
Anthemideae (50)	10	Germacranolides, Eudesmanolides, Guaianolides, Helenanolides, Cadinanolides, Chrymoranolides
Arctoteae-Calenduleae (50)	1	Guaianolides
Cynareae (50)	8	Germacranolides, Elemanolides, Guaianolides, Eudesmanolides
Mutiseae (55)	1	Eudesmanolides
Cichorieae (75)	6	Germacranolides, Eudesmanolides, Guaianolides

* See Fig. 1 for structures of different types of sesquiterpene lactones.

selective alkylation of nucleophilic groups in enzymes (e.g. sulphydryl enzymes) which control cell division. Vernolepin, a eudesmanolide has been shown to inhibit phosphofructokinase, an enzyme which has many –SH groups [75].

Microbial growth-inhibitors (antibiotics). Some sesquiterpene lactones have been shown to possess anti-bacterial, -fungal or -helminthic properties [58]. The germacranolides, mikanolide and dihydromikanolide (Fig. 3), from *Mikania monagasensis* inhibit the growth in culture, of a bacterium, *Staphylococcus aureus* and also of a yeast, *Candida albicans* [59]. Helenalin, a helenanolide common in species of *Helenium*, was shown to exhibit activity against the human pathogenic fungi, *Trichophyton mentagrophytes*, *T. acriminatum* and *Epidermophyton* sp. [60]. Parthenin, the major lactone from *Parthenium hysterophorus* was reported to inhibit sporangial germination and zoospore mobility in *Sclerospora graminicola*; such activity against the conidial development of *Aspergillus flavus* was lacking [61].

Chemoprophylaxis by lactones in schistosomiases. The wood oils of the Brazilian trees, *Eremanthus elaegnus*, *Vanillosmopsis erythropappa* and *Mosquinea velutiva* (Compositae) contain lactones that inhibit skin penetration by cercariae of the trematode, *Schistosoma mansoni*. Analysis of the wood oils indicated that the sesquiterpene lactones, eremanthine, costunolide and β-cyclocostunolide (Fig. 4) were the active principles. Dihydro-α-cyclocostunolide which lacks an exocyclic methylene group on the lactone ring was found to be inactive [18]. Recently, a novel germacranolide, goyazenolide, isolated from *Eremanthus goyazensis* was also shown to have schistosomicidal properties [44]. It was suggested that the activity of the schistosomicidal lactones may be related to inhibition of sulphydryl groups in cercarial enzymes.

Allergic contact dermatitis in Man. Sesquiterpene lactones from species of the Compositae, Lauraceae, Magnoliaceae and from the liverwort *Frullania*, (Jubulaceae) have been shown to be a major class of allergens causing allergic contact dermatitis in humans [45–50]. Over 80 sesquiterpene lactones were used in patch tests to determine their allergenic potential, and the presence of an α-methylene group, exocyclic to the γ-lactone, was shown to be the principal immunochemical requisite for the production of dermatitis [52, 54]. One of the allergenic lactones tested was the pseudoguianolide, parthenin, the major allergen in *Parthenium hysterophorus*. This extraordinarily aggressive weed was accidentally introduced into India from the Americas in 1956 and in certain cities of India, e.g. Poona, allergic contact dermatitis from *P. hysterophorus* has become an important dermatological and public health problem. A preponderance of males, in comparison to females and children affected by contact with the weed is so far unexplained. Among other plants (Table 3), responsible for dermatitis, are tiny epiphytic liverworts of the genus, *Frullania* which cause dermatitis in forest-workers who handle the bark of trees [20, 46, 53]. The sesquiterpene lactone, frullanolide identified in these epiphytic plants has been shown to be a potent sensitizer. Many varieties of *Chrysanthemum* [49, 55, 56] *Costus Absolute*, a perfume material derived from *Saussurea lappa* [51] and laurel oil, from *Laurus nobilis* [53] are sources of dermatitis and sesquiterpene lactones have been implicated in each instance (Table 4 presents structures). Certain persons may thus

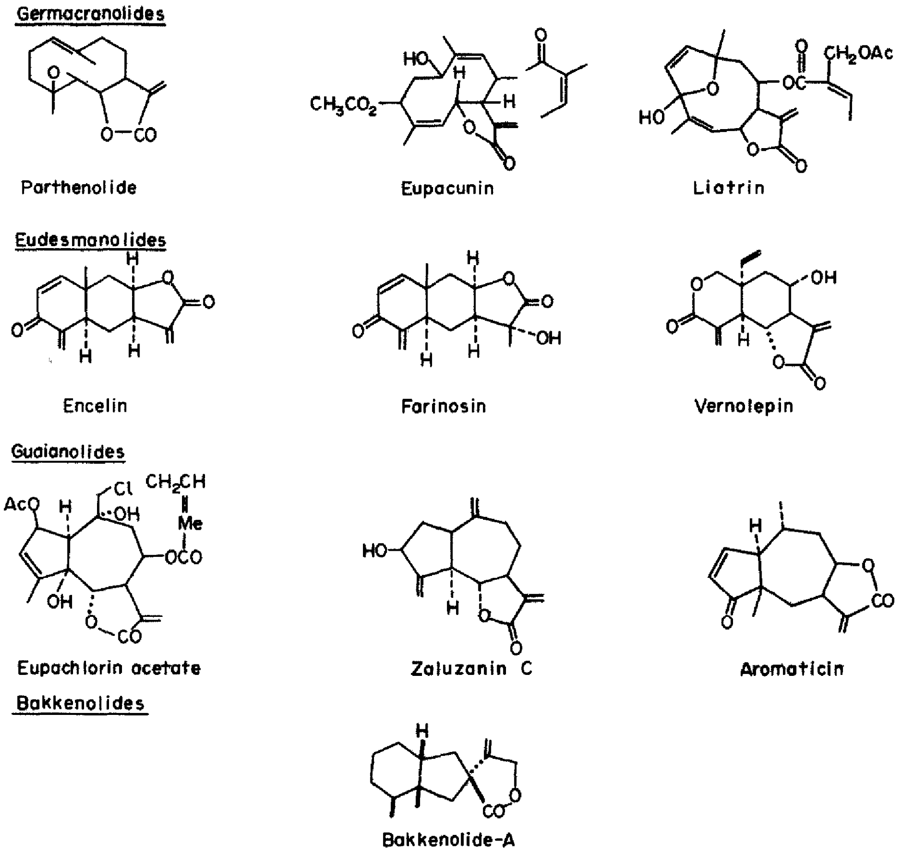


Fig. 2.

Table 2. Sesquiterpene lactones demonstrated to have antitumor and cytotoxic activity*

Compound†	Plant source	Tumor-system‡ assayed	Ref.
Germacranolides			
Ridentin	*Artemisia* sp.	WI/H.EP-2	[28]
Parthenolide			
Tamaulipin-A	*Ambrosia confertiflora*	WI/H.EP-2	[28]
Tamaulipin-B			
Chamissonin diacetate	*Ambrosia chamissonis*	KB	[23]
Eupacunin	*Eupatorium cuneifolium*	KB	[23]
Liatrin	*Liatris* sp.	KB	[23]
Elephantopin	*Elephantopus elatus*	KB/OS/WM	[23, 26]
Elephantin			
Eupatolide	*Eupatorium formosanum*	H.EP-2	[31, 39]
Molephantin	*Elephantopus millis*	H.EP-2	[36]
Phantomolin		H.EP-2	[40]
Deoxyelephantopin	*Elephantopus carolinianus*	WI	[34]
Guaianolides			
Eupachlorin acetate	*Eupatorium* sp.	KB	[23]
Deacetoxymatricarin	*Achillea lanulosa*	WI/H.EP-2/W-18Va2	[28]
Canin	*Artemisia cana*	WI/H.EP-2/W-18Va2	[28]
Arteglasin-A	*Artemisia douglasiana*	WI/H.EP-2/W-18Va2	[28]
Zaluzanin-C	*Zaluzania robinsonia*	PS	[43]
Pseudoguaianolides			
Helenalin	*Helenium autumnale*	KB/PS/H.EP-2	[36–38]
Helenalin derivatives		KB/PS/H.EP-2	[36, 38]
Aromaticin	*Helenium aromaticum*	KB	[23]
Mexicanin I	*Helenium mexicanum*	KB	[23]
Plenolin	*Baileya pleniradiata*	H.EP-2	[33]
Augustibalin	*Balduina angustifolia*	H.EP-2	[32]
Hymenoflorin	*Hymenoxys gradiflora*	LZ/PS	[42]
Ambrosin	*Hymenoclea salsola*	PS	[41]

Table 2—(*continued*)

Compound†	Plant source	Tumor-system‡ assayed	Ref.
Eudesmanolides			
α-Santonin	*Artemisia* spp.	WI/H.EP-2/W-18Va2	[28]
Vulgarin	*Artemisia vulgaris*	WI/H.EP-2/W-18Va2	[28]
Ludovicin	*Artemisia ludoviciana*	WI/H.EP-2/W-18Va2	[28]
Encelin }	*Encelia farinosa*	WI/H.EP-2/W-18Va2	[28]
Farinosin }		WI/H.EP-2/W-18Va2	[28]
Vernolepin	*Vernonia hymenolepsis*	KB	[23]
Bakkenolides			
Bakkenolide-A	*Petasites albus* *P. hybridus* *P. fragrans*	H.EP-2	[29]

* Sesquiterpene lactones known to be actineoplastic agents and reviewed by Hartwell and Abbott (1969) [22] are not included in this table. † Refer to Fig. 3 for structures. ‡ Code for tumor systems assayed follows that of Hartwell and Abbott (1969): H.EP-2—Human epidermoid carcinoma of larynx; KB—Human epidermoid carcinoma of the nasopharynx. Cell cultures; PS—P-388 lymphocytic leukemia. Mouse; WI—Walker carcinosarcoma 256. Ascites. Rat; WA—Walker carcinosarcoma 256. Rat; WM—Walker carcinosarcoma 256. Intramuscular; WI—38-Human diploid fibroblasts; W—18Va2—Simian virus 40-transformed cells of human origin; LZ—Leukemia L-210. Mouse (subcutaneous).

cross-react by skin contact allergy to such diverse plants and plant products as ragweed (*Ambrosia*), liverwort (*Frullania*), horticultural plants (*Chrysanthemum*), perfumes (*Saussurea*), weeds (*Parthenium* etc.) and vegetables (*Cichorium* etc.) from a common denominator, viz. a content of sesquiterpene lactones in the plant and plant products.

All the known allergenic sesquiterpene lactones contain an exocyclic α-methylene function which may conjugate with sulphydryl groups of proteins in cells by a Michael-type addition to form complete antigens capable of producing cell-mediated contact allergic reactions [54].

Insect feeding deterrents. Experimental evidence that sesquiterpene lactones provide resistance to insect feeding has been demonstrated by a study of the composite, *Vernonia* [57]. Larval feeding experiments were conducted on *Spodoptera eridania*, *S. frigiperda*, *Diacrisia virginia*, *Trichoplusia ni* and *S. ornithogalli* to determine whether the feeding preference of the 6 species was related to the presence of glaucolide-A (Fig. 5). Supplementing the agar medium with glaucolide-A, the major lactone in numerous species of *Vernonia* [57], resulted in greatly reduced larval feeding; feeding was inversely proportional to the concentration of glaucolide-A in the medium. Furthermore, these insects selected *Vernonia flaccidifolia* medium (which lacks glaucolide-A) in preference to the same diet containing the lactone. It was suggested that, in the course of evolution, these compounds have been selected quantitatively and qualitatively in response to herbivore pressure [57].

Vertebrate poisoning. Livestock-poisoning from foraging on bitter tasting plants of the Compositae is well documented in agricultural literature [62–65]. For example, *Hymenoxys odorata* (bitterweed) is an important livestock toxicant that affects primarily sheep and goats; annual losses in Texas are reported to be in millions of dollars [62, 64]. Recent chemical studies on *Hymenoxys odorata* have shown that hymenovin (Fig. 6), the major sesquiterpene lactone in populations of *H. odorata* from Texas, is the toxin involved in the death of sheep [64]. Similar poisoning (vomiting disease in sheep) has been noted among sheep grazing on South African species of *Geigeria* which contain the compound vermeerin [66]. It was suggested that the sesquiterpene lactone toxicant may alter the microbial composition of

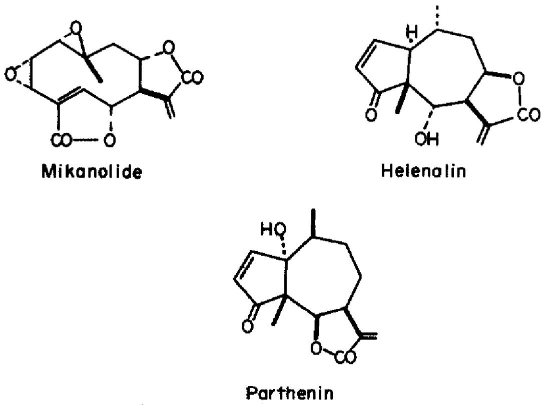
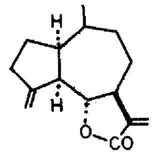
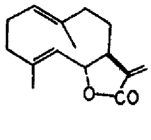


Fig. 3.

Table 3. Plants of the family Compositae which have been reported to cause contact dermatitis [54]

Achillea millefolium, *Ambrosia* spp., *Anthemis nobilis*, *Arctotheca calendulaceum* (*Cryptostemma*), *Arnica montana*, *Artemisia* spp., *Aster multiflorus*, *Buphthalmum salicifolium*, *Cassinea aculeata*, *Centaurea americana*, *Chrysanthemum*, *Cichorium endivia*, *C. intybus*, *Cosmos bipinnatus*, *Cynara scolymus*, *C. cardunculus*, *Dahlia* sp., *Erigeron canadensis* (*Leptilon*), *Eupatorium serotinum*, *Gaillardia* sp., *Galinsoga parviflora*, *Haplopappus ciliata* (*Prionopsis*), *Helianthus annuus*, *Helenium autumnale*, *H. microcephalum*, *H. tenuifolium*, *Helipterum charsleyae*, *Heterotheca subaxillaris* (*Chrysopsis*), *Hieracium auricula*, *Humea elegans*, *Inula brittanica*, *I. graveolens*, *Iva angustifolia*, *I. microcephala*, *I. xanthifolia*, *Lactuca sativa*, *L. sativa* var. *longifolia*, *Matricaria chamomilla*, *Olearia* spp., *Oxytenia acerosa*, *Parthenium argentatum*, *P. hysterophorus*, *Pyrethrum* spp. (*Chrysanthemum*), *Rudbeckia hirta*, *Rutidosis helichrysoides*, *Saussurea lappa*, *Solidago serotina*, *S. virga aurea* (sic), *Tagetes* spp., *Tanacetum vulgare*, *Taraxacum officinale*, *Telekia* sp. (*Buphthalmum*), *Vernonia baldwinii*, *Xanthium californicum*, *X. canadense*, *X. chinese*, *X. spinosum*, *X. strumarium*.


Eremanthine


Costunolide

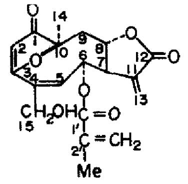

Goyazenolide

Fig. 4.

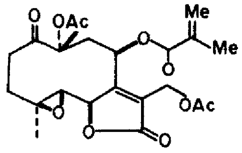
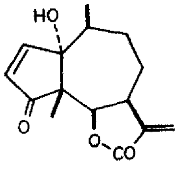
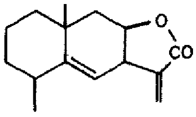
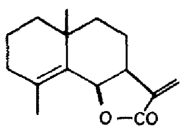
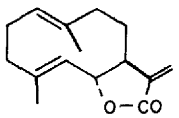
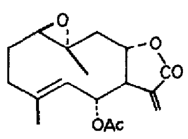
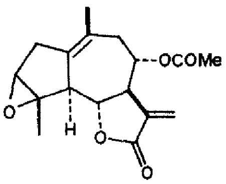

Glaucolide-A

Fig. 5.

the rumen and thus affect vital metabolic functions [64].

Besides their toxicity to sheep and goats, plants containing lactones when eaten by dairy cattle impart a bitter taste to their milk which is thus rendered unpalatable [62]. The lactone tenulin (Fig. 6) a constituent of *Helenium amarum* imparted a bitter taste to milk after oral administration to a lactating cow [65]. Table 5 lists some plants of the Compositae which are known to be toxic to livestock and the sesquiterpene lactones known to be present. These lactones have not necessarily been demonstrated to be the poisonous agents.

Table 4. Some sesquiterpene lactones reported to cause allergic contact dermatitis in humans

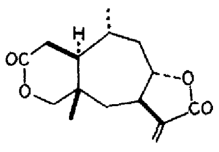
Compound	Plant source	Refs.
 Parthenin	*Parthenium hysterophorus*	[50]
 Alantolactone	*Inula helenium* *I. racemosa*	[46, 47, 54]
 Frullanolide	*Frullania tamarisci*	[20, 46, 53]
 Costunolide	*Saussurea lappa* *Laurus nobilis*	[51, 53]
 Pyrethrosin	*Chrysanthemum* spp.	[49, 55]
 Arteglasin-A	*Chrysanthemum indicum*	[56]

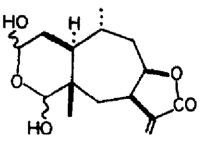
Plant-growth inhibitors (phytotoxins). A variety of sesquiterpene lactones of different skeletal types has been reported to show plant growth regulatory activity [68]. Heliangine, the major germacranolide of *Helianthus tuberosus*, inhibits the elongation of *Avena* coleoptile sections but promotes adventitious root formation of *Phaseolus* cuttings [69]. Promotion of adventitious root formation was reduced by the addition of cysteine or by hydrogenation of the exocyclic methylene group [69].

Vernolepin, an actineoplastic agent from *Vernonia hymenolepis*, inhibits growth (20–80%) of wheat coleoptile sections. Inhibited sections, when washed and subsequently treated with indole-3-acetic acid, responded to the auxin, but the degree of elongation was determined by prior treatment with vernolepin. Administered simultaneously, increasing amounts of auxin reduced the inhibitory effect of vernolepin [70]. Similar results were noted for parthenin on *Phaseolus vulgaris* [71] and the crop plant, *Eleusine coracana* [72].

The sesquiterpene lactones, arbusculin-A, achillin, desacetoxymatricarin, viscidulin-B and -C obtained from *Artemisia tridentata* var. *vaseyana* and other species of *Artemisia* were shown to inhibit lateral root growth but to stimulate respiration in *Cucumis sativum.* [73].

Alantolactone was shown to be a potent inhibitor of seed germination and of seedling growth. It was postulated that the lactone inhibits the enzymes associated with the degradation of starch (amylases) and of protein (proteases), but there is no evidence to support this. It


Vermeerin


Hymenoxin

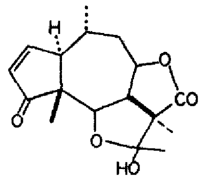

Tenulin

Fig. 6.

Table 5. Sesquiterpene lactones present in species of Compositae reported to be poisonous to livestock

Plant*	Compounds present†		Refs.
Hymenoxys odorata	Hymenolide Hymenoxyin Odoratin Paucin Vermeerin Hymenovin	Sheep/occasionally cattle	[62, 68]
Hymenoxys richardsonii	Vermeerin Psilotropin	Sheep/occasionally cattle	[64]
Helenium autumnale	Helenalin Mexicanin-E Bigelovin Tenulin Isotenulin	Sheep/cattle	[62, 63]
Helenium microcephalum	Helenalin Isohelenalin	Extremely poisonous to cattle/sheep	[62]
Helenium amarum	Amaralin Helenalin Tenulin	Sheep/goats/horses/rabbits/ milk bitter in cattle	[62, 64]
Parthenium hysterophorus	Parthenin Ambrosin Hymenin	Milk bitter in cattle	[67]
Geigeria africana	Vermeerin	Vomiting disease in sheep	[64, 66]
Baileya multiradiata	Fastiglin-C	Sheep/goats/rabbits	[63]
Xanthium strumarium	Xanthumin	Swine/cattle/sheep/horses	[62, 63]
Psilotrophe sparsiflora	Psilotropin	Sheep	[63]

* Plants of the Compositae for which the sesquiterpene lactone chemistry is not known, but are reported to be poisonous are not included (see Ref. [62] and [63]). † For individual structures of sesquiterpene lactones and references refer to [1].

was further suggested that the presence of *Inula* and other sesquiterpene lactone-containing plants in the agricultural plots might reduce the percentage of crop seeds [74].

MECHANISM OF ACTION OF SESQUITERPENE LACTONES

An examination of sesquiterpene lactones that exhibit growth inhibitory properties indicates that the following structural configurations are at least the principal requirements for biological activity:

(1) the presence of an exocyclic methylene conjugated to a γ-lactone;

(2) the presence of a functional group, such as an epoxide, hydroxyl, chlorohydrin, unsaturated ketone or *O*-acyl adjacent to the α-CH_2 of γ-lactone which can enhance the reactivity of the conjugated lactone toward biological nucleophiles.

As noted previously [17, 26, 54] the inhibitory action of sesquiterpene lactones results from the presence of highly electrophilic functional groups. These selectively alkylate by Michael-type addition to sulphydryl proteins, specifically thiol groups in preference to other nucleophiles.

Detailed investigations on the biological activities of sesquiterpene lactones of different skeletal type which is presently quite meagre, should provide useful information in our understanding of the adaptive role of these compounds in plants and contribute to an overall understanding of their activities in related disciplines of medicine, pharmacology and botany.

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