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Review Article

Plants and Plant Products that Induce Contact Dermatitis

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Key Word Index: Dermatitis; Plant Products; Plant Induced Contact Dermatitis.

Abstract

A detailed review of mechanical irritants, stinging nettles, phototoxic compounds and contact allergens causing dermatitis in men is presented. The producing plants and their dermatitis causing constituents are listed. The chemical structures and the botanical sources of primary irritants are also discussed.

Introduction

The production of dermatitis by contact is a highly effective defence mechanism exhibited by many plants, and poses a clinical problem both for the physician and the veterinary surgeon. Dermatitis can result from contact with living, damaged, or processed plant materials, and may manifest itself in the patient at

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once, a few hours after contact, or may not occur until the second or subsequent exposure as in the case of the allergens. Recent chemical and pharmacological investigations into natural product induced dermatitis have enabled the various plants and plant products to be classified into five major groups. Recognition of the type of agent involved is important from a clinical point of view. These groups comprise the mechanical irritants, the stinging nettles, the phototoxic compounds, the allergens, and the primary irritants. An understanding of the mechanisms of action of these substances may eventually lead to a greater understanding of the biochemistry of inflammation states and also pain production in mammalian skin.

Mechanical irritants

Several plant species are able to elicit characteristic dermatoses by means of small, easily detachable rough hairs or bristles [1], or by means of acicular calcium oxalate crystals [1, 2].

Many of the Boraginaceae, including *Borago*, *Echium*, *Lycopsis*, *Pentaglottis*, *Pulmonaria*, and *Symphytum* species are covered with course, stiff trichomes. These hairs are able to penetrate the skin and induce dermatitis [1]. *Cornus sanguinea* L. (Cornaceae), known as the dogwood, bears unusual T-shaped trichomes which produce erythema and urticaria when the leaf is rubbed on the skin [1]. *Malpighia urens* (Malpighiaceae) also bears hairs that can induce skin irritation. This plant was once thought to be a stinging nettle, but is now known to belong to the class of mechanical irritants [3]. The awns of barley and other cereal grasses are also known for their irritant properties. The effect is produced mechanically, and the dermatitis resembles that produced by various tropical palms that bear hook-like hairs [1]. An occupational dermatitis in pickers of the fruit of *Opuntia ficus-indica* L. (Mill.) and *Opuntia cochinillifera* (Cactaceae), known as prickly pears, has been termed sabra dermatitis [4]. This condition is caused by the penetration of the skin by glochidia, the small barbed bristles present in the areoles of the cacti [4,5].

Minute needle-shaped calcium oxalate crystals are present in the tissues of many plants [6, 7], where they are thought to be waste products of cellular metabolism. Their presence in the dry outer scales of daffodil (*Narcissus* species) and hyacinth (*Hyacinthus* species) bulbs is responsible in part for the condition known as lily rash, and hyacinth itsch [2]. An allergic sensitivity may co-occur, especially to *Narcissus* species [2]. The nature of the allergen is at present unknown.

Stinging nettles

The nettles have a highly specialised ability to evoke dermatitis. The plants are characterised by the presence of hypodermic syringe-like emergences [8, 9] which are capable of penetrating the skin and injecting a small amount of toxin. The effects produced range from mild skin irritation as in the case of the common British nettle (*Urtica dioica* L., Urticaceae), to painful severe dermatitis and even death [3, 10]. Plant bearing stinging hairs have been found in four plant fami-

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Table I
Plants that bear stinging hairs [3, 11]

Family	Genera			
Urticaceae	*Girardina*	*Hesperocnide*	*Nanocnide*	*Urera*
	Gyrotaenia	*Laportea*	*Obetia*	*Urtica*
Loasaceae	*Blumenbachia*	*Cevallia*	*Fuertesia*	*Loasa*
	Caiophora	*Eucnide*	*Gronovia*	
Euphorbiaceae	*Acidoton*	*Cnidoscolus*	*Pachystilidium*	*Sphaerostylis*
	Cnesmone	*Dalechampia*	*Platygyna*	*Tragia*
Hydrophyllaceae	*Wigandia*			

lies: the Urticaceae, Loasaceae, Euphorbiaceae, and Hydrophyllaceae (see Table I).

The stinging hair is a tapered elongated cell, constricted just below the tip. It has a bulbous base which is embedded in a multicellular sheathing pedestal. The tip of the hair is readily sheared off on slight contact to produce the hypodermic needle, which then penetrates the skin and injects its contents [3]. Of the few species studied, most have been found to bear hairs with a silicaceous tip. However, the stinging hairs of *Tragia* species have a calcium oxalate tip. This is ejected from the cell on contact and penetrates the skin. The initial sensation of pain is produced mechanically, but the skin reaction is due to the injected toxin [3, 9].

Little is known of the composition of the nettle toxins. Acetylcholine, histamine, and 5-hydroxytyptamine have been reported as being present in extracts of *Urtica dioica*, *Urtica parviflora* and *Girardinia heterophylla* [12, 13, 14, 15]. These investigations were pharmacological and chromatographic only, and a much more rigorous chemical analysis is indicated. An investigation of the mechanism of action of the sting toxin from *Urtica urens* demonstrated that the effect of the sting could be reproduced by pricking the skin in the presence of acetylcholine and histamine [16]. In addition, substances with the pharmacological activity of acetylcholine, histamine, and 5-hydroxy-tryptamine have been detected in *Laportea moroides* [10], but in this case attempts to reproduce the effects of the sting were not successful. The toxin of this species produces pain, inflammation, sweating, and piloerection [10].

Although not a stinging nettle, cowhage (*Mucuna pruriens* DC Leguminosae) and other *Mucuna* species [17] bear trichomes on their seed pods that can elicit intense pruritis and inflammation on penetration of the skin [18]. A proteinase known as mucunain has been shown to occur on the exterior surface of the barbed trichomes. This enzyme is responsible for the intense pruritis and together with the mechanical effect of the hairs is probably responsible for subsequent dermatitis [19].

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Phototoxic compounds

Many compounds are known that become photo-activated on exposure to a certain waveband of light which may be in the ultra-violet or near visible range. This can occur *in vitro*, but if allowed to occur on living skin the compound may thereby become either a primary irritant or an allergen. In the plant kingdom, the only compounds that have been reported to evoke photodermatitis are furocoumarins [20, 21].

The naturally occurring furocoumarins are phototoxic compounds and after activation act as primary irritants. Since no allergic mechanism is involved all individuals may be expected to react on the first exposure if the concentration of the phototoxic principle and light intensity is sufficient. The severity of the response is also increased by high humidity [20, 21]. The course of the skin reaction resembles that of sunburn, and characteristically leaves pigmentation which may persist for several months. The precise mode of action of the furocoumarins is not completely understood. It has been suggested that photobinding to epidermal DNA and ribosomal RNA is involved in the waveband 320–370 nm in the ultra-violet region [22, 23]. A structure-activity study [23] has demonstrated that of the naturally occurring furocoumarins, psoralen is the most active phototoxic agent. Xanthotoxin was found to be only one third as active and bergapten a quarter as active as psoralen. The synthetic 8-methylpsoralen was almost six times as potent as psoralen (see Fig. 1).

The furocoumarins have only a limited distribution in the plant kingdom, having been found in the families Moraceae, Umbelliferae, Rutaceae, Rosaceae, and Leguminosae [24]. Some of the more common furocoumarin containing species that have been found to elicit photodermatitis include:

Heracleum mantegazzianum	Umbelliferae	[24, 25]
Pastinaca sativa	Umbelliferae	[24, 26, 27]
Dictamnus albus	Rutaceae	[24, 27]
Phebalium argentium	Rutaceae	[28]
Ficus carica	Moraceae	[29]
Psoralea species	Leguminosae	[30]

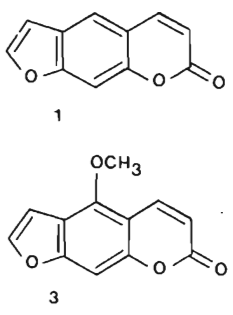

Figure 1

1. Psoralen
2. Xanthotoxin
3. Bergapten
4. 8-Methylpsoralen

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Contact allergens

The most frequent type of inflammatory skin condition induced by plants and plant products is allergic eczematous contact dermatitis [21]. Such a reaction can take many forms varying from a dry scaly erythema to a severe papular or vesicular inflammation with oedema [7, 20, 21]. Histologically, all forms are similar and resemble primary irritant dermatitis [20]. The plant metabolites responsible are low molecular weight compounds such as haptens. Susceptibility to sensitisation by contact allergens is genetically determined, and is related to race, sex, and possibly age. Sensitisation is also dependent on the sensitising potential of the allergen, the quantity, and method of exposure. Consequently, not all individuals are affected similarly [20, 21]. One of the most potent allergenic materials, urushiol from poison ivy, may induce sensitivity after the first exposure. The process of sensitisation takes between six and twenty-five days, after which time a flare may develop when residues of the allergen react with newly sensitised tissue. This is termed a 'late reaction'. Subsequent exposure to the allergen will elicit a clinical response after a delay of 24–48 hours, but may occur as soon as 8 hours or as late as 120 hours after exposure depending on the allergen and the degree of exposure [20]. Some allergens of low sensitising potential may be seemingly innocuous for many years. Many cases of occupational dermatitis are caused by prolonged repeated exposure to such substances. Once sensitisation has occurred, subsequent exposure to a sufficient concentration of the allergen will induce dermatitis. The course of the reaction is then similar to that produced by more potent sensitisers. The primary allergen in cases of occupational dermatitis can often be identified by means of patch testing. However, if the primary allergen is of plant origin, identification may be difficult or impossible. Many plants contain a complex mixture of potential allergens, any one or all of which will produce dermatitis when applied to the skin of a sensitised individual. It is not unusual for sensitivity to several compounds to occur simultaneously. A potential allergen may also elicit dermatitis in an individual sensitised to a different but structurally related substance, a phenomenon known as cross-sensitivity. Furthermore, compounds that are structurally related to an allergen may not themselves be allergenic, and yet they may be capable of producing dermatitis. Such secondary allergens are known as elicitors. Patch testing can demonstrate secondary allergenicity, but the status of the primary allergen needs to be ascertained by suitable *in vivo* methods [20].

Urushiol is an ill-defined term used to denote the allergenic principles of poison ivy and related species of the Anacardiaceae. These substances are mixtures of homologous long chain phenolic compounds. Similar 'urushiols' have been isolated from the fruit pulp of *Ginkgo biloba* L. (Ginkgoaceae) and also from species of the family Proteaceae (see Fig. 2 and Table II).

Although reference has been made to the vesicant properties of urushiols, these compounds are not primary irritants at dose levels that evoke the characteristic skin reaction for which they are known [59]. Nevertheless, both the sap of *Anacardium occidentale* and the fruit pulp of

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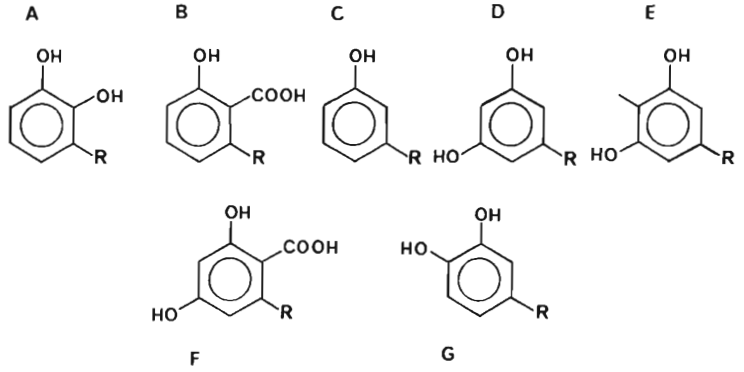

R

1 $(CH_2)_8 \cdot CH_3$
2 $(CH_2)_{10} \cdot CH_3$
3 $(CH_2)_2 \cdot CH{=}CH \cdot (CH_2)_6 \cdot CH_3$
4 $(CH_2)_{12} \cdot CH_3$
5 $(CH_2)_{14} \cdot CH_3$
6 $(CH_2)_7 \cdot CH{=}CH \cdot (CH_2)_5 \cdot CH_3$
7 $(CH_2)_9 \cdot CH{=}CH \cdot (CH_2)_3 \cdot CH_3$
8 $(CH_2)_7 \cdot CH{=}CH \cdot CH_2 \cdot CH{=}CH \cdot (CH_2)_2 \cdot CH_3$
9 $(CH_2)_7 \cdot CH{=}CH \cdot CH_2 \cdot CH{=}CH \cdot CH_2 \cdot CH{=}CH_2$
10 $(CH_2)_7 \cdot CH{=}CH \cdot CH_2 \cdot CH{=}CH \cdot CH{=}CH \cdot CH_3$
11 $C_{15}H_{31}$
12 $C_{15}H_{29}$
13 $C_{15}H_{27}$
14 $C_{15}H_{25}$
15 $(CH_2)_{16} \cdot CH_3$
16 $(CH_2)_7 \cdot CH{=}CH \cdot (CH_2)_7 \cdot CH_3$
17 $(CH_2)_9 \cdot CH{=}CH \cdot (CH_2)_5 \cdot CH_3$
18 $(CH_2)_7 \cdot CH{=}CH \cdot CH_2 \cdot CH{=}CH \cdot (CH_2)_4 \cdot CH_3$
19 $C_{17}H_{35}$
21 $C_{17}H_{33}$
20 $C_{17}H_{31}$
22 $C_{17}H_{29}$
23 $(CH_2)_{18} \cdot CH_3$
24 $(CH_2)_9 \cdot CH{=}CH \cdot (CH_2)_7 \cdot CH_3$
25 $C_{19}H_{35}$

Figure 2

Ginkgo biloba have been shown to have a primary irritant effect [60, 61].

The sesquiterpene lactones form another major group of naturally occurring contact allergens. These compounds have been found in the families Umbelliferae, Magnoliaceae, Lauraceae, Aristolochiaceae, Compositae, and in a genus of liverworts in the family Jubilaceae [62]. Allergenic sesquiterpene lactones have been found in the Compositae, Jubilaceae, and Lauraceae. In areas where certain species of the family Compositae are found, sensitisation to sesquiterpene lactones may be widespread. The compounds are concentrated in fragile glandular trichomes [63] and also on pollen grains. As small particles, both the glands and the pollen may be widely distributed by the wind. This type of allergy is quite distinct from hay fever which is caused by the protein constituents of the pollen exine [21].

Sesquiterpene lactones can be classified according to their hydrocarbon skeletons. Allergenic lactones based on guaiane, eudesmane, germacrane, and pseudoguaiane have been reported (see Fig. 3). Recent structure activity studies show that a γ-lactone with an exocyclic α-methylene group is a partial requirement for activity [62, 64, 65]. Over 250 sesquiter-

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Table II
The botanical sources of the urushiols

Source	Compound (see Fig. 2)	Literature
ANACARDIACEAE		
Anacardium occidentale L.	B5, B6, B8, B9	[31, 32, 33]
	C5, C6, C8, C9	[34]
	D5, D6, D8, D9	[31, 35]
	E5, E12, E13, E14, E19–E22	[36]
Gluta renghas L.	A20	[37]
Holigarna arnottiana HOOK f.	A21	[38, 39]
Melanorrhoea usitata WALL	G21	[38]
Metopium toxiferum KRUG and URB.	A11–A14, A20–A22	[40]
Pentaspadon motleyi HOOK f.	B21	[41]
Pentaspadon officinalis HOLMES	B18	[42]
Semecarpus anacardium L.	A13	[43]
Semecarpus heterophylla BL.	A7	[44]
Semecarpus travancorica BED.	A21	[38, 45]
Smodingium argutum E. MEY	A11, A12, A16, A18, A19, A22	[46]
Toxicodendron diversilobum (T. and G.) GREENE	A11–A14, A19–A22	[40, 47]
Toxicodendron radicans (L.) KUNTZE	A5, A6, A8, A9, A19–A22	[40, 46, 48, 49]
Toxicodendron striatum (RUIZ and PAVON)	Kuntze A5, A6, A8, A9	[50]
Toxicodendron succedaneum (L.) KUNTZE	A11–A13, A19–A22	[38, 46]
Toxicodendron vernicifluum (STOKES)	Barkley A5, A6, A8, A10	[51]
Toxicodendron vernix (L.) KUNTZE	A11–A14	[40]
GINKGOACEAE		
Ginkgo biloba L.	B6, C6, D6	[52]
	F4, F6	[53]
PROTEACEAE		
Cardwellia sublimis F. MUELL.	D5, D12, D15, D16, D25	[54]
Grevillea hilliana F. MUELL.	D4–D6, D15–D17, D23, D24	[54]
Grevillea banksii R. BR.	D2, D4–D7	[54]
Grevillea pteridifolia KNIGHT	D4–D7, D15	[54]
Grevillea pyramidalis	D7	[55]
Grevillea robusta A. CUNN.	D4–D7	[56, 57]
Hakea persiehana F. MUELL.	D4, D5, D15, D16	[54]
Opisthiolepis heterophylla L. S. SMITH	D4, D5, D12, D20	[54]
Persoonia elliptica R. BR.	D2–D4	[58]
Persoonia linearis ANDR.	D1–D3	[54]
Petrophila shirleyae F. M. BAIL	D6, D20	[54]

pene lactones have been chemically characterised in recent years and about 50 of these have been shown to elicit dermatitis in sensitised individuals (see Fig. 4). At least a further 100 are potential allergens by virtue of their structural features [62, 64], but have not yet been biologically tested.

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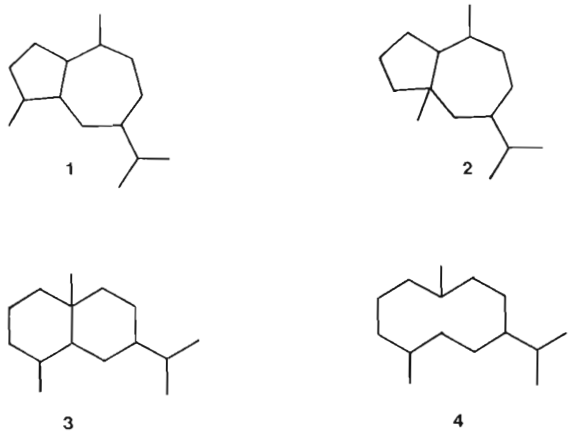

1. Guaiane
2. Pseudoguaiane
3. Eudesmane
4. Germacrane

Figure 3

The plant sources of immunologically active sesquiterpene lactones are given in Table III.

Certain naturally occurring quinones (see Fig. 5) constitute another group of allergens with a high sensitising potential [21, 75]. The incidence of quinone induced dermatitis is lower than might be expected, mainly because these compounds are found largely in the heartwood of mature trees. However, the most common cause of natural product induced dermatitis in Britain is the quinone primin from the leaves of *Primula obconica* Primulaceae [75]. The majority of the other quinones given in Fig. 5 are constituents of commercial timbers that were found to produce occupational dermatoses in woodworkers [76]. The plant sources of immunologically active quinones are given in Table IV.

Tulipalin A (Fig. 6) is the allergenic principle of *Tulipa* species [95, 96, 97], *Erythronium* species [95, 97, 98], and *Alstroemeria* species [95, 97, 99]. There is also evidence to suggest a much wider distribution of this compound in the Liliaceae and related families [95, 97]. Tulpalin A is a phytoalexin [100, 101]. It does not occur naturally, but is formed by means of an enzyme-induced hydrolysis of the glycoside tuliposide A when the plant or bulb is damaged. The condition evoked is known as tulip fingers [2].

The essential (or volatile) oils are complex mixtures of substances containing terpenoids, phenols, acids, alcohols, and ethers. Generally, volatile oils have low allergenic potential, and may in some cases be weak primary irritants also [20]. The more common allergenic constituents of the oils are summarised in Fig. 7.

Several other plant products are known to give rise to allergic reactions. These substances belong to various chemical classes, including the alkaloids, steroids, flavonoids, cyclic ethers, and the lichen compounds. These miscellaneous allergens are summarised in Fig. 8, and their botanical sources given in Table V.

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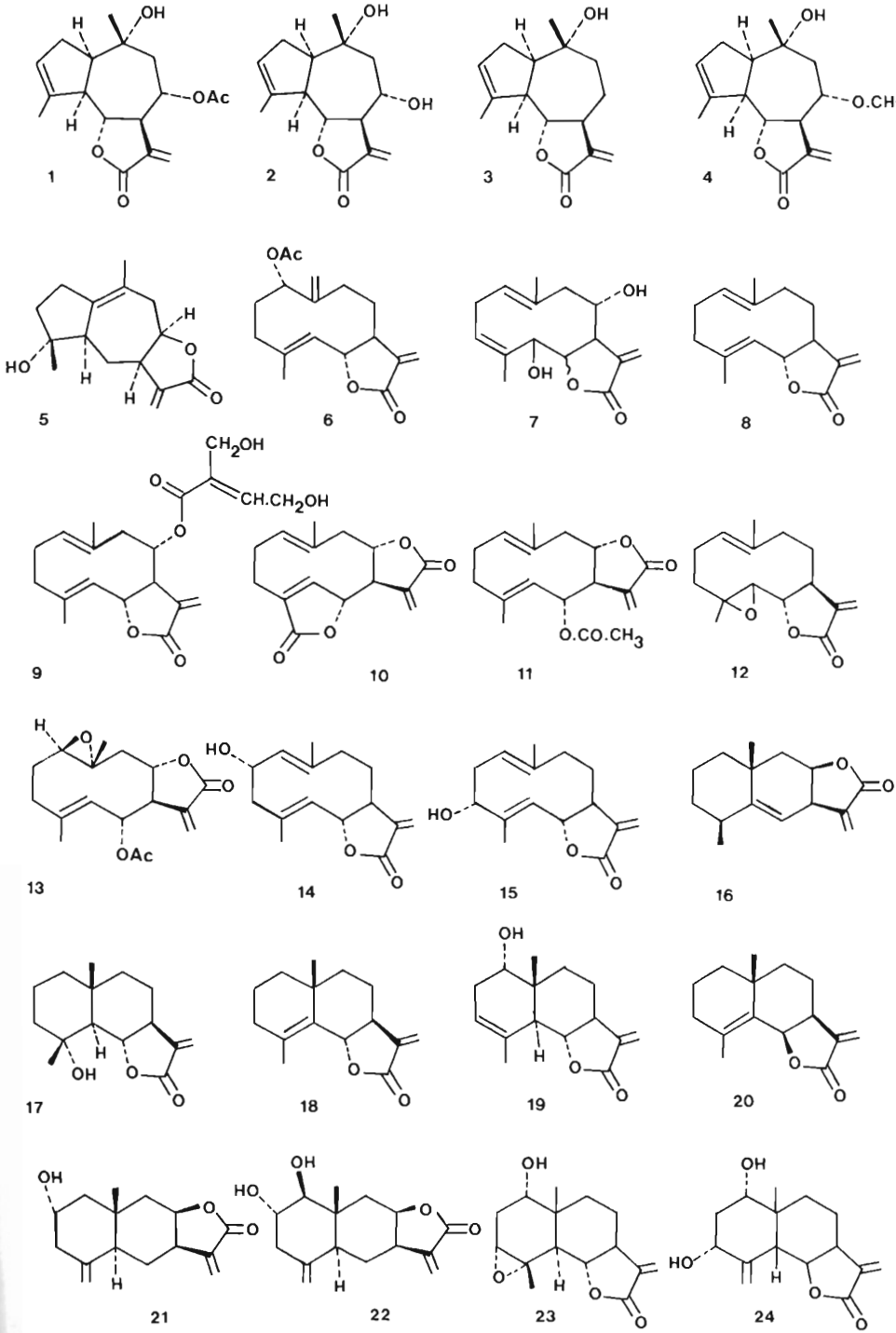

Figure 4

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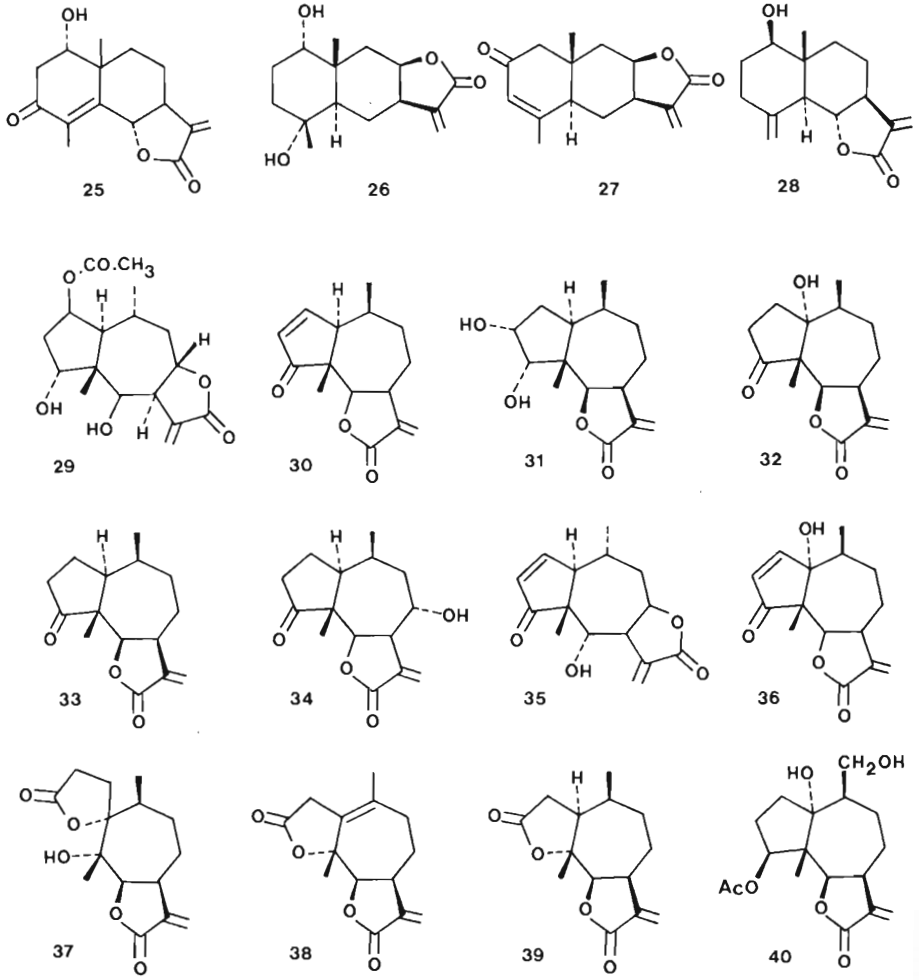

1. Cumambrin A
2. Cumambrin B
3. 8-Deoxycumambrin
4. Formylcumambrin B
5. Pseudoivalin
6. Artemorin acetate
7. Chamissonin
8. Costunolide
9. Eupatoriopicrin
10. Isabelin
11. Laurenobiolide
12. Parthenolide
13. Pyrethrosin
14. Tamaulipin A
15. Tamaulipin B
16. Alantolactone
17. Arbusculin A
18. Arbusculin B
19. Douglanine
20. (–) Frullanolide*
21. Ivalin
22. Ivasperin
23. Ludovicin A
24. Ludovicin B
25. Ludovicin C
26. Microcephalin
27. Pinnatifidin
28. Reynosin
29. Alternilin
30. Ambrosin
31. Ambrosiol
32. Coronopilin
33. Damsin
34. Desacetylconfertiflorin
35. Helenalin
36. Parthenin
37. Psilostachyin A
38. Psilostachyin B
39. Psilostachyin C
40. Tetraneurin E

* (+) Frullanolide also active

Figure 4, cont.

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Table III
Botanical sources of allergenic sesquiterpene lactones (62–74)

Plant species	Sesquiterpene Lactones present (see Fig. 4)
COMPOSITAE	
Ambrosia acanthicarpa HOOK.	34, 39
A. ambrosoides (CAV.) PAYNE	33
A. arborescens LAM.	33, 37, 39
A. artemisiifolia L.	10, 32, 33, 37
A. chamissonis (LESS.) GREENE	7
A. chenopodiifolia PAYNE	33, 37, 39
A. confertiflora DC	14, 15, 34, 37, 38
A. cordifolia (GRAY) PAYNE	39
A. cumanensis	30, 32, 33, 36, 37, 38, 39
A. deltoidea (TORR.) PAYNE	33, 39
A. dumosa (GRAY) PAYNE	12, 31, 32, 37
A. hispida PURSH.	30, 33
A. maritima L.	30, 33
A. peruviana WILLD.	39
A. psilostachya DC	10, 31, 32, 33, 36, 37, 38
A. pumilia GRAY	34, 37, 39
A. tenuifolia GREH. and GODR.	37
Artemisia arbuscula NUTT.	17, 18
A. balchanorum KRASCH	8
A. ludoviciana NUTT.	19, 23, 24, 25
A. nova NELS	1, 2, 3, 4
A. tripartita RYDB. ssp. *rubicola* BEETLE	3
A. verlotorum LAMATTE	6
Balduinia angustifolia (PURSH.) ROBINS	35
Chrysanthemum cinerariaefolium VIS.	13
Chrysanthemum coccineum WILLD.	13
C. parthenium L.	12, 28
C. tanacetum L.	12
Eupatorium cannabinum L.	9
Franseria dumosa GRAY	30
Gaillardia megapotamica (SPRENG.) BAKER	35
G. multiceps GREENE	35
G. pinnatifida TORR.	35
Helenium alternifolium (SPRENG) CABR.	29
H. aromaticum (HOOK.) BAILEY	35
H. autumnale L.	35
H. campestre SMALL	35
H. laciniatum GRAY	35
H. mexicanum H. B. K.	35
H. microcephalum M. A. CURT ex GRAY	35
H. pinnatifidum (NUTT.) RYDB.	27
H. quadridentatum LABILL.	35
H. vernale WALT.	35
Hymenoclea spp.	30

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Plant species	Sesquiterpene Lactones present (see Fig. 4)
Inula helenium L.	16
Iva acerosa (NUTT.) JACKSON	32
I. asperifolia LESS.	22
I. cheiranthifolia H. B. K.	21
I. imbricata WALT.	21
I. microcephala NUTT. VAR A.	21
I. microcephala NUTT. VAR B.	5, 26
I. nevadensis M. E. JONES	32, 36
I. texensis JACKSON	22
I. xanthifolia NUTT.	32
Parthenium confertum var. *lyratum*	40
P. hysterophorus L.	30, 36
P. incanum H. B. K.	30, 32
P. integrifolium L.	40
Saussurea lappa CLARKE	8
JUBILACEAE	
Frullania nisquallensis SULL.	20
F. tamarisci (L.) DUM	20
F. dilatata (L.) DUM.	(+) Frullanolide
LAURACEAE	
Laurus nobilis L.	11

Primary irritants

Many species of plants are capable of evoking primary irritant dermatitis [7, 138, 139]. Before about 1968, primary irritants of the plant kingdom were described as being generally not chemically identified [7]. More recently, the chemical nature of several groups of irritants has been elucidated, particularly those from the families Euphorbiaceae and Thymelaeaceae [140]. The mechanism by which irritants exert their effect is as yet only poorly understood. In general, it is believed that inflammation arises in response to tissue damage, although more specific biological actions such as agonism of an endogenous hormone or transmitter [141] may account for the inflammatory actions of some of the *Euphorbia* irritants.

The skin reaction to primary irritants occurs within a short period of time after contact. Unlike allergenic substances, primary irritants will affect all subjects on the first exposure if the concentration is sufficient [20, 21].

Several members of the family Ranunculaceae cause dermatitis when crushed on the skin [139, 142, 143, 144, 145]. The irritant properties of the plants have been ascribed to protoanemonin (2, Fig. 9) which has been isolated from several *Ranunculus* and *Pulsatilla* species [142, 143, 145, 146]. Protoanemonin is produced jn damaged plant tissues from the hlucoside ranunculin (1, Fig. 9) by means of a simple enzyme induced cleavage [143].

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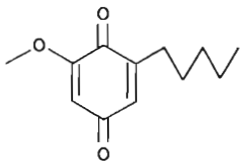
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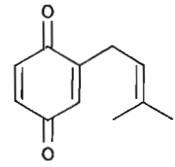
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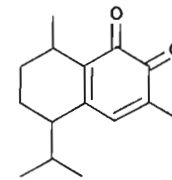
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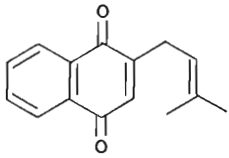
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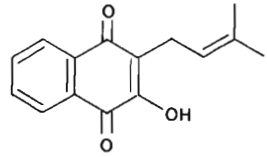
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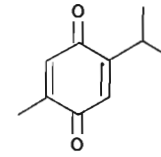
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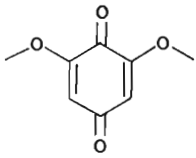
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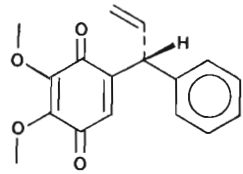
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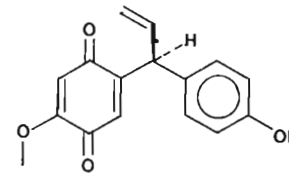
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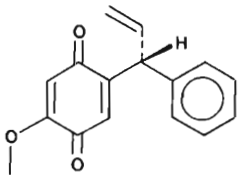
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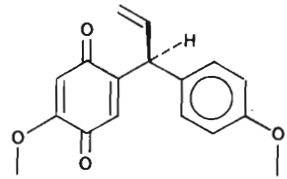
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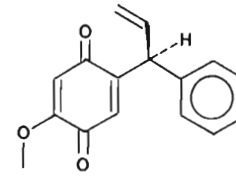
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1. Primin
2. 2-(3-Methyl-2-butenyl)-1,4-benzoquinone
3. Mansonone A
4. Deoxylapachol
5. Lapachol
6. Thymoquinone
7. 2,6-Dimethoxy-1, 4-benzoquinone
8. R-3,4-Dimethoxydalbergione
9. S-4-Methoxy-4´-hydroxydalbergione
10. R-4-Methoxydalbergione
11. S-4,4´-Dimethoxydalbergione
12. S-4-Methoxydalbergione

Figure 5

Capsaicin (3, Fig. 9) and the related capsaicinoids are responsible for the pungent taste of chili peppers (*Caipsicum minimum* and *C. fructescens* Solanaceae) and in addition are powerful skin irritants [123, 147, 148].

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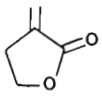
Table IV
Plant sources of immunologically active quinones

Quinone	*Plant source(s)*	Literature
1. Primin	*Primula obconica* HANCE Primulaceae	[77, 78, 79]
2. 2-(3-Methyl-2-butenyl)-1,4-benzoquinone	*Phagnolon saxitale* CASS. Compositae	[76, 80]
3. Mansonone A	*Mansonia altissima* CHEV. Sterculiaceae	[81, 82, 83]
4. Deoxylapachol	*Tectona grandis* Verbenaceae	[76, 84]
5. Lapachol	*Tectona grandis* Verbenaceae	[76, 85]
	Paratecoma, Tabebuia spp. Bignoniaceae	[76, 85]
6. Thymoquinone	*Libocedrus decurrens* Pinaceae	[86, 87]
7. 2,6-Dimethoxy-1,4-benzoquinone	*Bowdichia nitida* BENTH. Leguminosae	[88, 89]
8. R-3,4-Dimethoxydalbergione	*Machaerium* spp. Leguminosae	[89, 90, 91, 92, 93]
9. S-4-Methoxy-4′-hydroxy-dalbergione	*Dalbergia* spp. Leguminosae	[89, 94]
10. R-4-Methoxydalbergione	*Dalbergia* spp. Leguminosae	[93, 94]
11. S-4,4′-Dimethoxydalbergione	*Dalbergia* spp. Leguminosae	[94]
12. S-4-Methoxydalbergione	*Dalbergia* sp. Leguminosae	[93]



Tulipalin A

Figure 6

Capsaicin induces erythema but no blistering in mammalian skin [149] and a report has been made concerning possible allergenic activity [21]. The gingerols (4, Fig. 9) and shogaol (5, Fig. 9) of ginger (*Zingiber officinalis* Zingiberaceae) are also capsaicin-like compounds and are contained in the rhizome of this species which is said to be rubefacient [150, 151, 152].

Certain complex volatile oils also have mild skin irritant properties Amongst the more well known volatile oil producing plants, the oils of cajuput, clove, eucalyptus, nutmeg, pumiliopine, rosemary, thyme, and turpentine have been reported to induce inflammation of the skin [123]. Not all of the constituents of these oils have been tested for irritancy, but it is known that α-pinene, limonene, and eugenol (2, 4 and 5, Fig. 7) are primary irritants [108, 109]. Safrole (6, Fig. 9) is an irritant constituent of the oil of several plant species including *Sassafras albidum* of the Lauraceae, and certain *Ocotea* species from the same family [123]. Star anise (*Illicium verum*, Magnoliaceae) oil contains safrole as an active irritant component, as well as α-pinene and limonene [107, 123].

Ambrosic acid (7, Fig. 9), a sesquiterpene isolated from the pollen of *Ambrosia artemisiifolia* Compositae has also been described as an irritant compound [153], but details of biological tests employed were not given.

A few plants are known that contain proteolytic enzymes in their sap. Contact between the sap and the skin can result in a mild dermatitis [7, 21, 154]. The enzymes papain (from *Carica papaya*

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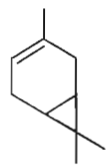

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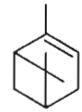

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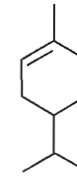

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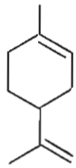

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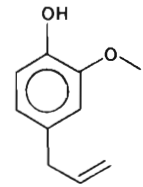

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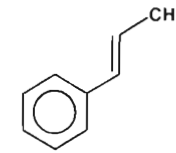

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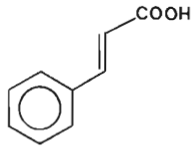

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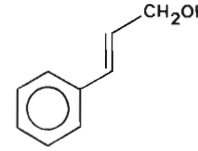

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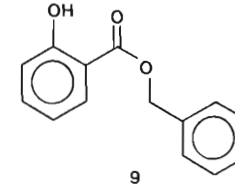

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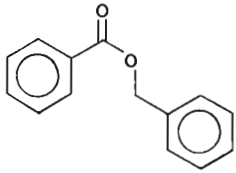

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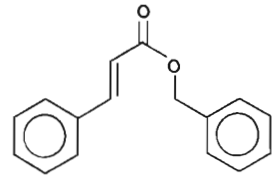

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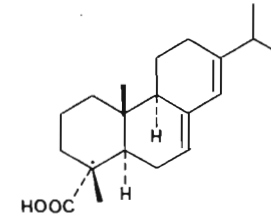

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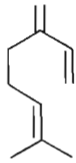

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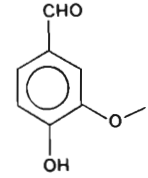

14

1. Δ3-carene
2. α-Pinene
3. α-Phellandrene
4. Limonene
5. Engenol
6. Cinnamic aldehyde
7. Cinnamic acid
8. Cinnamyl alcohol
9. Benzyl salicylate
10. Benzyl benzoate
11. Benzyl cinnamate
12. Abietic acid
13. Myrcene
14. Vanillin

Figure 7

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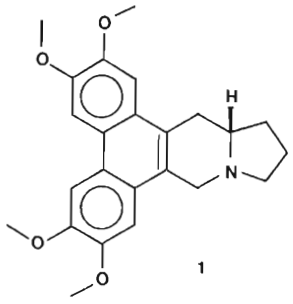

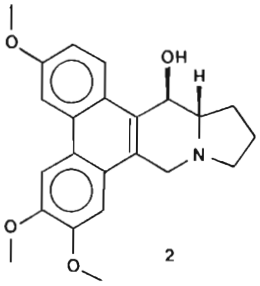

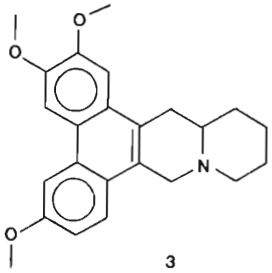

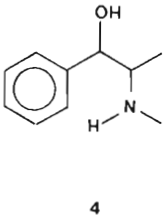

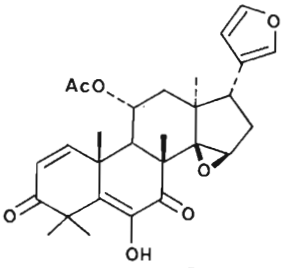

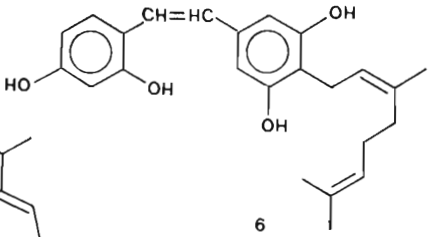

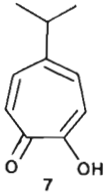

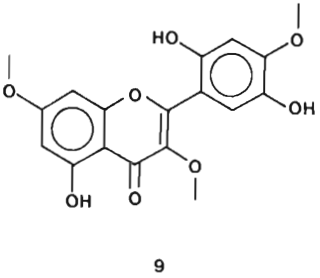

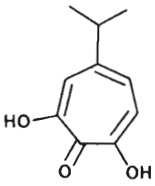

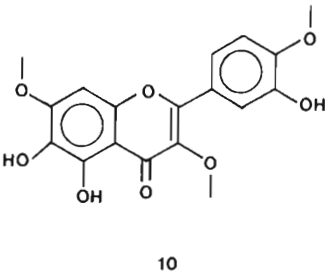

1. Tylophorine
2. Tylophorinine
3. Cryptopleurine
4. Ephedrine
5. Anthothecol
6. Chlorophorin
7. γ-Thujaplicin
8. 7-Hydroxy-4-isopropyltropolone
9. Oxyayanin A
10. Oxyayanin B

Figure 8

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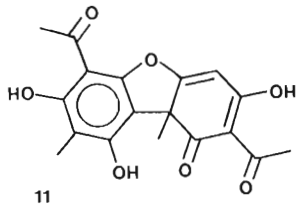

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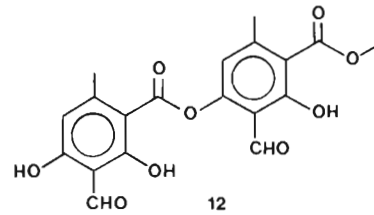

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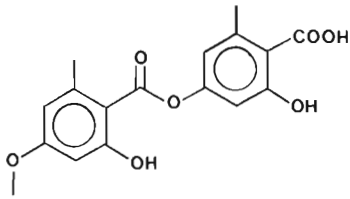

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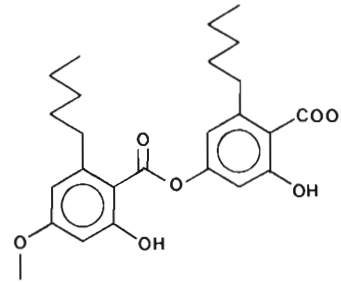

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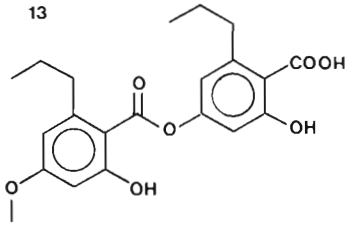

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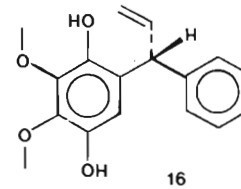

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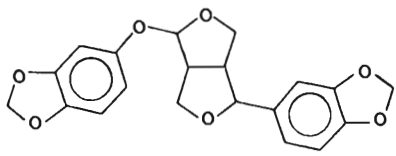

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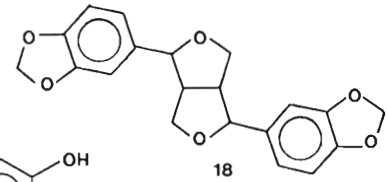

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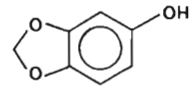

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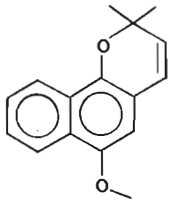

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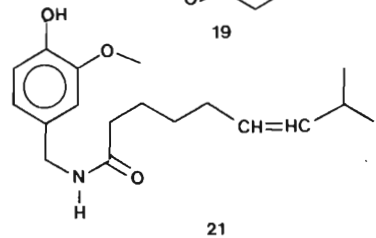

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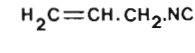

22

11. d-Usnic acid
12. Atranorin
13. Evernic acid
14. Perlatolic acid
15. Divaricotic acid
16. R-3,4-Dimethoxydalbergione quinol
17. Sesamolin
18. Sesamin
19. Sesamol
20. Lapachone
21. Capsaicin
22. Allyl isothiocynate

Figure 8, cont.

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Table V
Botanical sources of miscellaneous allergens

Compound	Botanical source	Literature
1. Tylophorine	*Ficus* spp. Moraceae *Tylophora, Cynanchum* spp. Asclepiadaceae	[115, 116, 117, 118]
2. Tylophorinine	*Tylophora* spp. Asclepiadaceae	[117, 119]
3. Cryptopleurine	*Cryptocarya pleurosperma* WHITE et FRANCIS Lauraceae	[120, 121, 122]
4. Ephedrine	*Ephedra* spp. Gnetaceae	[6, 123]
5. Anthothecol	*Khaya anthotheca* DC Meliaceae	[93, 124, 125]
6. Chlorophorin	*Chlorophora excelsa* BENTH. et HOOK. f. Moraceae	[70, 82, 126]
7. γ-Thujaplicin	*Thuja plicata* Cupressaceae	[127]
8. 7-Hydroxy-4-isopropyl tropolone	*Thuja plicata* Cupressaceae	[127]
9. Oxyayanin A	*Distemonanthus benthamianus* Leguminosae	[128]
10. Oxyayanin B	*Distemonanthus benthamianus* Leguminosae	[128]
11. d-Usnic acid	(Widely distributed in lichens)	[129, 130, 131, 132]
12. Atranorin	(Widely distributed in lichens)	[129, 130, 131, 132]
13. Evernic acid	*Evernia, Ramalia, Usnea* spp.	[129, 130, 131, 132]
14. Perlatolic acid	*Parmelia, Cladonia* spp.	[129, 130, 131, 132]
15. Divaricotic acid	*Evernia* spp.	[129, 132]
16. R-3,4-Dimethoxy-dalbergione quinol	*Machaerium* spp.	[90, 92]
17. Sesamolin	*Sesamum indicum* L. Pedaliaceae	[133]
18. Sesamin	*Sesamum indicum* L. Pedaliaceae	[133]
19. Sesamol	*Sesamum indicum* L. Pedaliaceae	[133]
20. Lapachone	*Paratecoma, Tabebuia Stereospermum* spp. Bignoniaceae *Tectonis grandis* Verbenaceae	[85, 134, 135]
21. Capaicin	*Capsicum* spp. Solanaceae	[21]
22. Allyl isothiocyanate	*Brassica nigra* KOCH Cruciferae	[136, 137]

Caricaceae) ficin (from *Ficus* species, Moraceae) and bromelin (from *Ananas sativa*, Bromeliaceae) have been implicated in this type of skin reaction [7, 21, 154]. The protease, nepenthin, contained in the fluid of pitcher plants (*Nepenthes* species, Nepenthaceae) may also be capable of causing dermatitis [154].

Damage to the onion (*Allium cepa* Liliaceae) causes the release of lachrymatory propenylsulphenic acid (8, Fig. 9) [155]. The mild irritant properties of freshly cut or damaged onions [152] may in part be attributed to this compound. The irritant properties of other *Allium* species [138, 152] have been attributed to other sulphur containing compounds [138].

The mustard oils constitute a group of substances known chemically as the isothiocyanates. These compounds are a well defined and unique class of natural irritants which are produced by decomposition of glucosinolate glycosides

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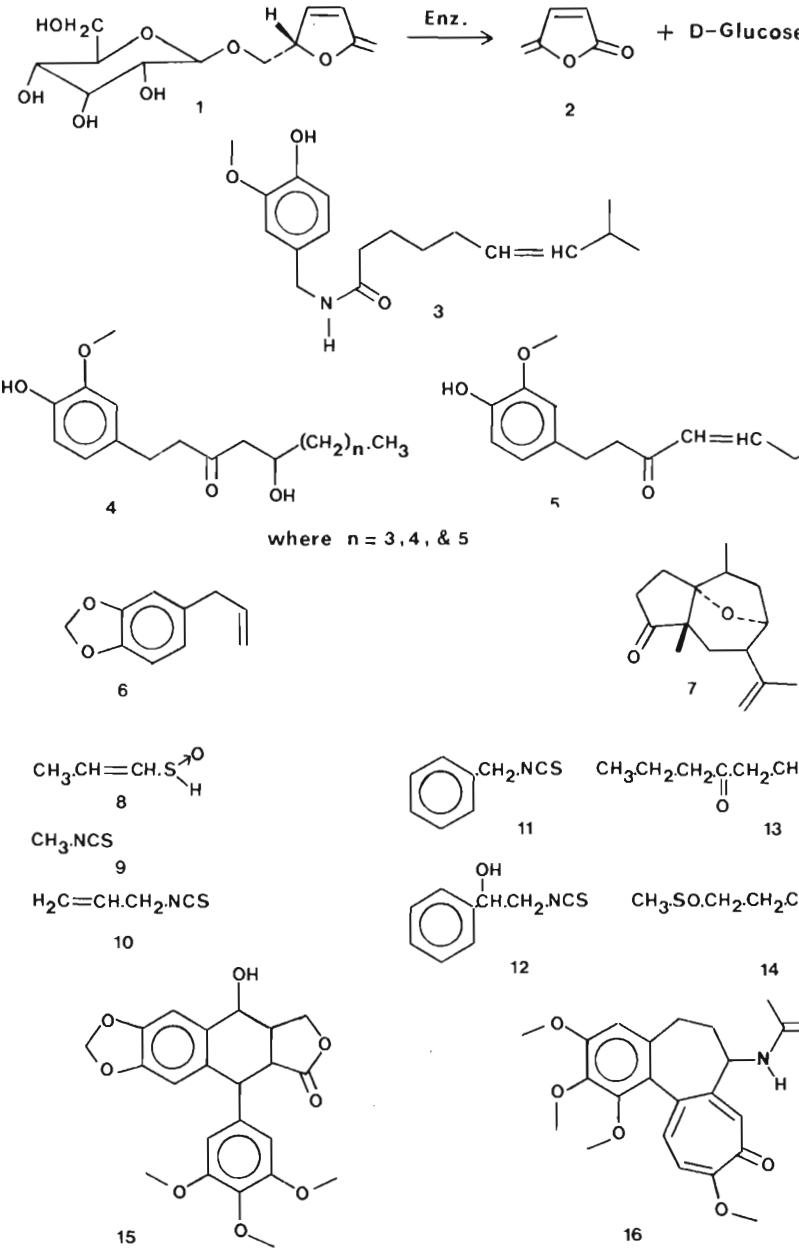

1. Ranunculin
2. Protoanemonin
3. Capsaicin
4. The gingerols
5. Shogaol
6. Safrole
7. Ambrosic acid
8. Propenylsulphenic acid
9. –14. Examples of isothiocyanates from natural sources
15. Podophyllotoxin
16. Colchicine

Figure 9

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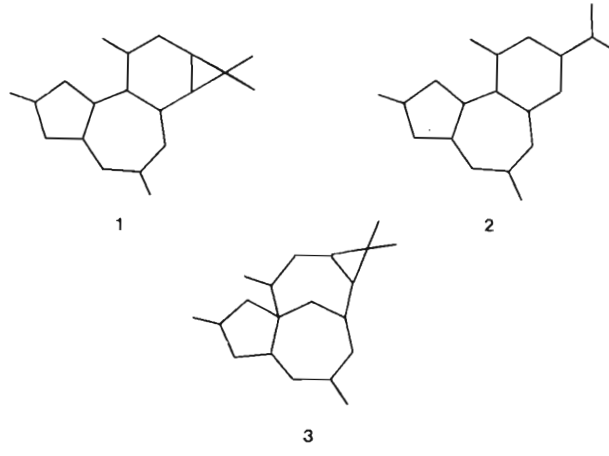
[136]. These glycosides occur in the plants as anions, usually as their potassium salts. When the plant is damaged the enzyme myrosinase is liberated which in the presence of moisture produces the mustard oils from their glycolsidal form. Chemically this reaction occurs by means of hydrolytic fission of the thioglucoside linkage followed by a Lossen-type rearrangement [136].

The various mustard oils are classified according to the structure of their side chains. Six groups have been recognised, being the alkyl saturated, hydroxy substituted, keto substituted, aromatic, methyl-thioalkyl and alkyl unsaturated (see 9–14, Fig. 9) [136, 156]. Glycosides of this type are distributed throughout the family Cruciferae and also in the Caricaceae, Capparidaceae, Resedaceae, Euphorbiaceae, Tovariaceae, Moringaceae, Limnanthaceae, Tropaeolaceae, Gyrostemmonaceae, and Salvadoraceae [136, 156]. The iso-thiocyanate function of the liberated mustard oils confers the vesicant and lachrymatory properties to these compounds [136].

Phodophyllum resin, derived from *Podophyllum peltatum* and *P. hexandrum* Berberidaceae, is a powerful irritant substance that has been used to remove warts from skin [123]. The biologically active principle of the resin is probably podophyllotoxin (15, Fig. 9). However, since this compound accounts for only 10–30 % of the resin [6], other irritant substances may be present. Podophyllum resin has also been reported to be allergenic [157]. Colchicine (16, Fig. 9) is a cytotoxic alkaloid present in the bulbs of the autumn crocus (*Colchicum autumnale* Liliaceae). The drug has been used as an analgesic in the treatment of gout [123]. It has also been demonstrated that application to mammalian skin will induce inflammation and hyperplasia [158].

Many species of the Euphorbiaceae and Thymelaeaceae contain a highly irri-



1. Tigliane 2. Daphnane 3. Ingenane

Figure 10

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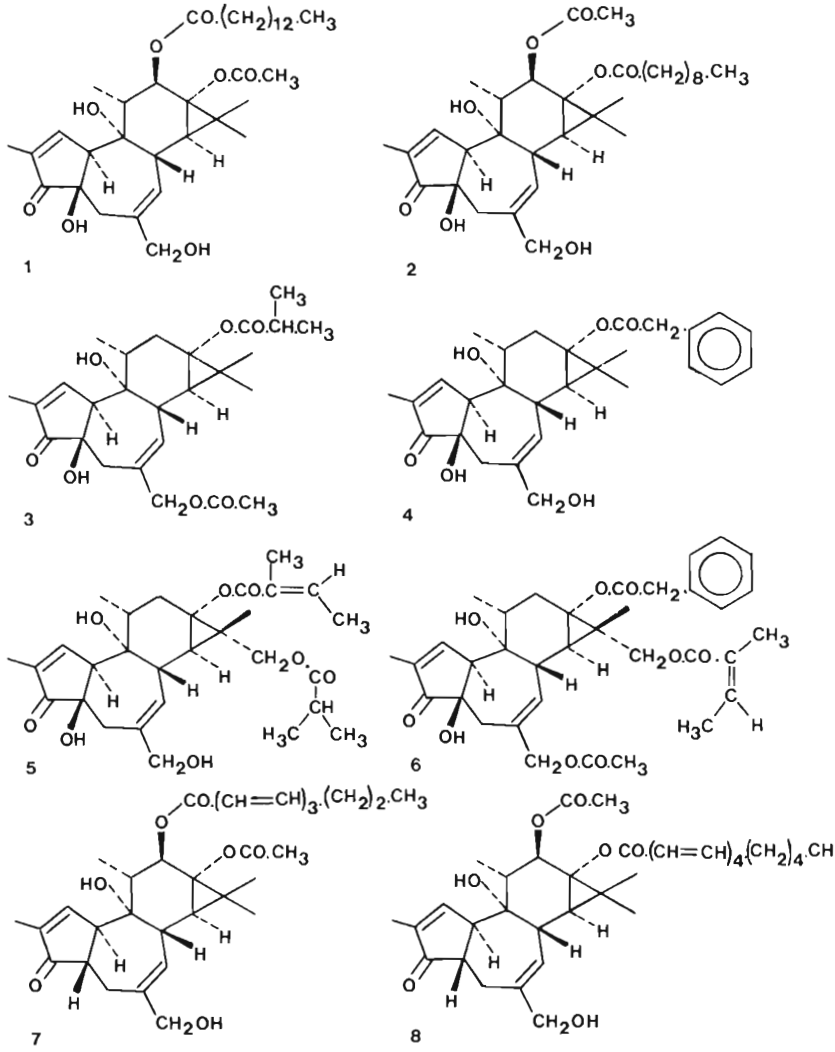
tant sap or latex [7, 138]. At one time, several of these plants were employed in medicine as counter-irritants or as purgatives. Recently the irritant principles of these plants have been shown to be esters of closely related diterpene polyols based on the tigliane, ingenane, and daphnane hydrocarbon skeletons (Fig. 10) [140].



1. 12-O-Tetradecanoylphorbol-13-acetate
2. 12-O-Acetylphorbol-13-decanoate
3. 12-Deoxyphorbol-13-(2-methylpropanoate)-20-acetate
4. 12-Deoxyphorbol-13-phenylacetate
5. 12-Deoxy-16-hydroxyphorbol-13-angelate-16-(2-methylpropanoate)-20-acetate
6. Candletoxin B
7. 4-Deoxyphorbol-12-(2,4,6-decatrienoate)-13-acetate
8. 4-Deoxyphorbol-12-acetate-13-(2,4,6,8-tetradecatetraenoate)

Figure 11

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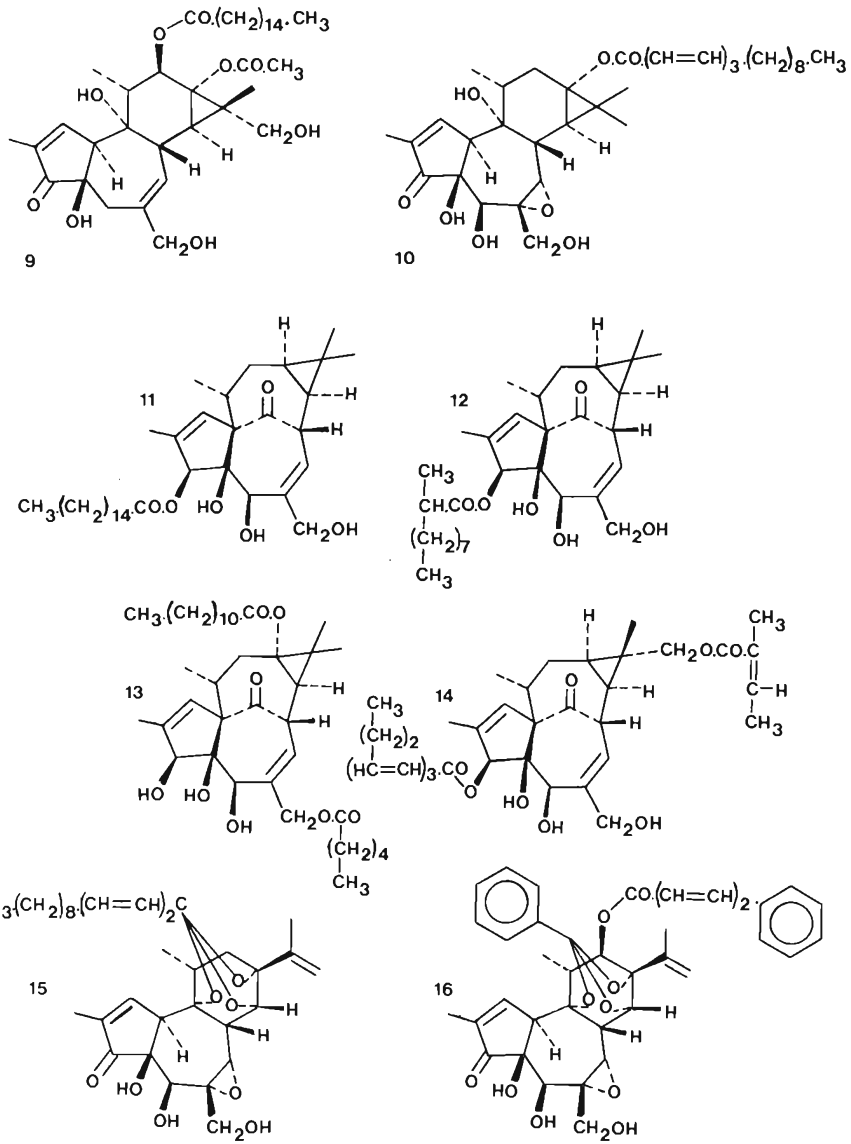

9. 16-Hydroxyphorbol-12-hexadecanoate-13-acetate
10. Mancinellin
11. 3-O-Hexadecanoylingenol
12. 3-O-(2-Methyldecanoyl)ingenol
13. 13-Oxyingenol-13-dodecanoate-20-hexanoate
14. 16-Oxyingenol-3-(2,4,6-decatrienoate)-16-angelate
15. Huratoxin
16. Mezerein

Figure 11, cont.

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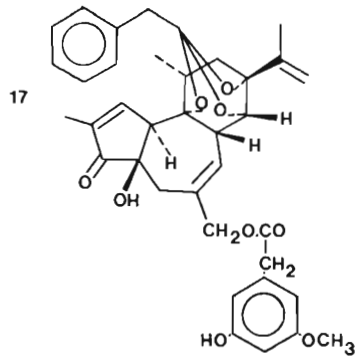
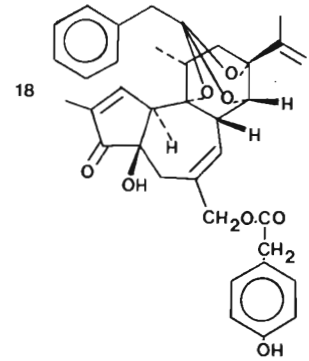


17. Resiniferatoxin



18. Tinyatoxin

Figure 11, cont.

The first compounds of this type to be isolated were esters of the tigliane polyol known as phorbol. This is a unique tetracyclic diterpenoid obtained originally from the oil and resin of seeds of *Croton tiglium* L. Euphorbiaceae [159]. Similar esters have been isolated from *Euphorbia* species and from *Sapium japonicum* Euphorbiaceae [160, 161, 162]. In addition, related tigliane polyols have been isolated from various species in the Euphorbiaceae. These include 12-deoxyphorbol [163, 164], 12-deoxy-16-hydroxyphorbol [165, 166], 16-hydroxyphorbol [167], and 4-deoxyphorbol. [160] The daphnanes are on the other hand tricylic diterpenoids. The cyclopropane ring system of the tigliane series is opened out to give an isopropylene side chain. The majority of the daphnanes occur as orthoesters [140], although O-acyl forms have been reported from *Euphorbia poissonii*, *E. resinifera*, and *E. unispina* [141, 168] Several species of the family Thymelaeaceae including *Daphne*, *Gnidium* and *Lasiosiphon* [140] produce daphnane ortho esters as also do the genera *Hippomane*, *Hura*, and *Excoecaria* in the family Euphorbiaceae [140]. Ingenane polyol esters have been isolated from species of the genera *Euphorbia* and *Elaeophorbia* [140]. Ingenol was the first polyol of this group to be obtained as a series of esters from *Euphorbia ingens* and *Euphorbia lathyris* [169, 170]. Similar compunds later isolated from other species of this genus include 5-deoxyingenol [171], 13-oxyingenol [172], and 16-hydroxyingenol [162].

The acute biological effects of compounds belonging to these groups include inflammation of the skin with oedema and hyperplasia [140]. On prolonged repeated application of certain of these compounds to mouse skin, promotion of tumours has been observed [173]. There are also reports that certain of these compounds exhibit antileukaemic activity [140]. Irritant compounds of these series have certain structural features in common. They exhibit a trans junction between the cyclopentane and cycloheptane rings A and B, and ester groups, which are essential for irritant activity, are variously located at the C-3, C-5, C-12, C-13, C-16, and C-20 positions. The mode

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Table VI
Botanical sources of some irritant tigliane, ingenane, and daphnane polyol esters

Source	Irritant ester (see Fig. 11)	Literature
EUPHORBIACEAE		
Aleurites fordii HEMSL.	9	[167]
Croton tiglium L.	1, 2	[159]
Euphorbia cooperi N. E. BR.	5	[165]
E. fortissima LEACH	3	[174]
E. ingens E. MEY	11, 14	[170]
E. kansui LIOU	13	[172]
E. lathyris L.	11	[169, 173]
E. poissonii PAX	3, 6, 17, 18	[166, 175, 176]
E. resinifera BERGER	3, 12, 17	[168, 178]
E. tirucalli L.	7, 8	[173, 178]
E. triangularis DESF.	3	[163]
E. unispina N. E. BR.	3, 4, 17, 18	[141, 175, 176]
Hippomane mancinella L.	10, 15	[179]
Hura crepitans L.	15	[180]
THYMELAEACEAE		
Daphne mezereum L.	16	[181]

of action of these potent irritants remains unknown at the present time, but it is probable that generally they induce inflammation by a specific effect at a membrane bound receptor site, as well as by tissue damage [141, 182].

Selected examples of irritant esters belonging to the tree major groups are given in Fig. 11, and their botanical sources are given in Table VI.

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