GREEN PLANTS THAT AFFECT HUMAN SKIN

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Allergic contact dermatitis in North America usually is associated with members of the Anacardiaceae such as Rhus radicans (poison ivy), R. diversilobum (Eastern oakleaf poison ivy) and R. vernix (poison sumac). The sensitizing compounds are alkylated dihydroxy phenols, and they also occur in Japanese lacquer (R. vernicifera), mango (Mangifera indica), cashew nut shell oil (Anacardium occidentale), and Indian marking nut (Semecarpus sp.). Goldstein (1968) has given an interesting account of cross sensitivity to members of the Anacardiaceae.

The subject of contact allergy from plants has been reviewed recently by Mitchell (1975).

Allergic contact dermatitis, also known as delayed hypersensitivity or Type IV cell-mediated hypersensitivity (Roitt 1971), is produced by contact of the skin with low-molecular weight chemicals which sensitize blood lymphocytes. In a sensitized individual, the appearance of dermatitis, on re-exposure to the chemical, is delayed in onset by one to two days. The clinical manifestations are erythematous maculopapular rashes or papulovesicular eruptions on exposed areas of the body. Sensitization to a specific chemical is determined usually by a patch test.

Our collaborative studies at the University of British Columbia* originated with cases of allergic contact dermatitis evoked by species of Frullania, a genus of epiphytic liverworts, in forest workers in British Columbia. Over the years there had been cases reported in France and the Pacific Northwest of North America (Bleumink et al 1976; LeCoulant & Lopes 1956, 1960, 1966; Mitchell et al 1969, 1971; Storrs et al 1976). A simultaneous chemical investigation, by Ourisson's group in France, of the allergens led to the identification of the major sensitizer (Knoche et al 1969; Mitchell et al 1970; Perold et al 1972). This turned out to be a sesquiterpene lactone which was named frullanolide (Fig 1). It was found to be accompanied by other closely related sesquiterpene lactones such as costunolide and arbusculin-β which were later on also shown to be allergenic (Asakawa et al 1976; Green et al 1972; Perold et al 1972). Sesquiterpene lactones are low molecular weight, colorless, bitter, lipophilic constituents of plants, and more than 500 have been isolated and identified from many species of plants, chiefly from the family, Compositae (Devon & Scott 1972; Yoshioka et al 1973). Many of them have been shown to be biologically active eg, anti-tumor, cytotoxic or antibiotic (Rodriguez et al 1976b). Their cytotoxicity is often associated with the presence in the molecule of an α-methylene-ϒ-lactone (Kupchan et al 1971; Lee et al 1973), or an unsaturated α,β-ketonic moiety (Lee et al 1971; 1973).

So far the major sources of the 200 to 300 known sesquiterpene lactones are species of Compositae (Devon & Scott 1972; Yoshioka et al 1973) and, in the light of the results with Frullania, dermatitis resulting

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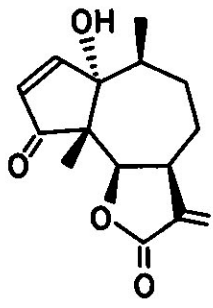
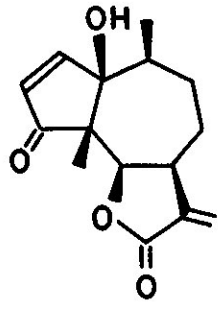


Parthenin



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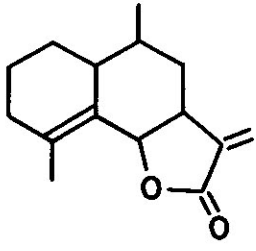
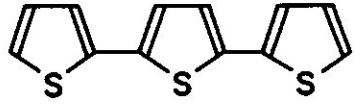
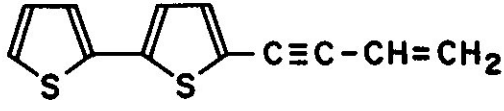


Frullanolide



α-Terthienyl



5-(3-Buten-1-ynyl)-2,2'-bithienyl

Fig 1. Structures of Parthenin, Hymenin, Frullanolide, α-terthienyl, and 5-(3-buten-1-ynyl)-2,2'-bithienyl.

from Compositae required a study. One of the 50 or more forest workers in British Columbia who had allergic contact dermatitis from Frullania also was discovered to be contact-sensitive to Chrysanthemum x morifolium (Mitchell et al 1970). Dermatitis caused by certain composites, eg, chrysanthemum, ragweed and tansy, has been known for many years (Greenhouse & Sulzberger 1933; Mitchell et al 1971; Nightingale 1931). Chrysanthemum x morifolium is the commonest reported cause of dermatitis from horticultural composites (Mitchell et al 1970, 1971). In West Germany, for instance, it is one of the most common causes of occupational contact dermatitis among gardeners and florists (Hausen & Schulz 1975, 1976) and one of the identified allergens was shown to be arteglasin-A, a sesquiterpene lactone of the guaianolide type (Hausen & Schulz 1975). About 60 species of Compositae, including well-known genera such as Ambrosia, Artemisia, Aster, Cosmos, Dahlia, Helianthus, Hieracium, Matricaria, Rudbeckia, Solidago, Tagetes and Xanthium, also have been reported to cause allergic contact dermatitis (Mitchell 1970). Sesquiterpene lactones, are distributed among all these groups with the exception of Tagetes. In an extensive study by our group, it was shown that a prerequisite for activity is a lactone moiety with an exocyclic -methylene function (Mitchell et al 1970). Reduction of the methylene to a methyl function results in loss of activity (Mitchell et al 1970). The allergenic properties of the sesquiterpene lactones, in other words, are correlated with their cytotoxic activities as shown by the work of others (Kupchan et al 1971).

Cross-sensitivity patterns to patch tests with crude plant extracts vary in sensitized individuals, and in general, highly sensitized individuals are found to show a wider spectrum of cross-sensitivity than weakly sensitized ones (Mitchell et al 1970; Hjorth & Roed-Peterson 1976).

Cross-sensitivity to specific plants is nothing more than a reflection of cross-sensitivity to specific sesquiterpene lactones, but the reasons for these differences between individuals are not obvious. Very few studies have been made of this interesting and complex phenomenon.

Pyrethrum, also known as Dalmatian or Persian insect powder, consists of dried flower heads of Chrysanthemum cinerarifolium and C. coccineum. It is an effective insecticide and is used in scabiecidal and anti-mosquito preparations. It may cause allergic eczematous contact dermatitis (Anon. 1936; Lord & Johnson 1947; McCord 1962; McCord et al 1921; Martin & Hester 1941; Mitchell et al 1972; Sequeira 1936; Sulzberger & Weinberg 1930; Sweitzer 1936). In a patient with allergic contact dermatitis from pyrethrum, pyrethrosin, a sesquiterpene lactone which does not have insecticidal properties, was shown to be the principal allergen of pyrethrum derived from species of Chrysanthemum (Mitchell et al 1972).

'Australian bush dermatitis' is a chronic dermatitis of exposed areas occurring in men living in the Australian bush (Burry et al 1973). Although the dermatitis appears to be evoked by Compositae, as evidenced by positive patch tests to ragweed (Ambrosia) and other species of Compositae, the causative species is not always known. Cases of dermatitis caused by the Compositae, Arctotheca, Cassinea, Inula, and Artemisia are often referred to as a bush dermatitis in Australia.

In 1974, at the University of British Columbia, we had reached a stage in our dermatological and phytochemical investigations of weed dermatitis where we could pinpoint, confidently, the chemical source of

delayed hypersensitivity to Compositae as the sesquiterpene lactones contained in these plants. Dr Arvind Lonkar, a dermatologist from Poona, India, drew our attention to the high and increasing incidence of allergic contact dermatitis in that city from a new weed, Parthenium hysterophorus. This member of the Compositae is native to the Caribbean Islands, Central America, the southern United States and parts of Argentina, Brazil and Bolivia. It is an aggressive weed of disturbed sites and, within the last 100 yr, has found its way to Africa, Australia and to Asia. It has spread to a serious extent in India where is poses a serious agriculture problem as well as a medical hazard (Towers et al, in press).

Parthenium hysterophorus was first noticed in Poona, as an adventive in 1956 and increasing numbers of cases of dermatitis were traced to exposure to it. The dermatitis affected primarily the exposed skin surfaces, ie, surfaces not usually covered by clothing, of agricultural laborers but an increasing number of city dwellers became affected as the plant spread into urban regions (Lonkar et al 1974).

Contact allergy to Parthenium develops from repeated contacts with plants or possibly its disseminated parts and, after sensitization, itching eruptions occur on exposed parts of the body particularly the upper eyelids, sides of the neck, parts of the face, V-of the neck, fronts of elbows and backs of knees (Lonkar et al 1974). The skin shows vesiculation with exudation and pruritus is intense. As the dermatitis progresses lichenification, impetiginization, fissuring of the skin, and various pigmentary changes follow.

Allergic contact dermatitis from Parthenium had been known in rural workers in the southern United States for many years but, with urbanization and mechanization of farming practices, it has declined in incidence according to an experienced Texas dermatologist (J. B. Howell, in litt 1976).

In India, clinically and patch test established cases of Parthenium dermatitis have so far been reported from Poona (Lonkar et al 1974), Bangalore (Subba Rao et al 1976) and Delhi (J. S. Pasricha & D. N. Shivpuri in litt). Suspected cases of the dermatitis from Parthenium have also been reported anecdotally from other places, particularly in the states of Maharashtra and Karnataka where the weed is widespread. Initially, typical patients were adult males engaged in outdoor work, particularly farmers. In recent years, white-collar workers, bankers, doctors, policemen etc, were found to develop the allergy (Subba Rao et al 1976). A predilection of the dermatitis for adult males has been observed in America and India and is so far unexplained. Children before puberty are spared (Lonkar et al 1974), and no cases of Parthenium dermatitis were encountered in either women or children in the course of clinical studies in Bangalore (P. V. Subba Rao in litt).

The major sesquiterpene lactone in most populations of P. hysterophorus is the pseudoguaianolide, parthenin (Fig 1). Some plant populations from southern Texas and those from southern Bolivia and central Argentina contain the diastereomer, hymenin, (Fig 1) as the major lactone (Rodriguez 1975). Of 10 Indian patients sensitized to Parthenium and to parthenin none reacted to hymenin (Subba Rao et al unpubl.) indicating that it is not only the α-methylene lactone moiety that is important but also the configuration about the bridge carbon bearing a hydroxyl group. This would suggest that the double bond in the cyclopentenone ring may participate in the allergenic reaction(s). Helenalin

and tenulin, sesquiterpene lactones which bear cyclopentenone moieties, undergo a Michael-type addition reaction with the sulfhydryl groups of reduced glutathione and L-cysteine (Lee et al 1977). In the case of helenalin the α-methylene-ϒ-lactone system also acts as an alkylating center. We have found that parthenin forms as least two adducts with cysteine under relatively mild conditions (Picman et al, unpubl.). In one of these adducts it is the α-methylene function which is involved and, in the other, both the α-methylene as well as the double bond of the cyclopentenone ring. With sesquiterpene lactones which do not contain cyclopentenone rings, or other reactive centers, eg alantolactone, it is the α-methylene group of the lactone ring which reacts with sulfhydryl groups and is presumably involved in the allergic reaction. Obviously a great deal of study of the interaction of these compounds with membrane proteins of skin cells is needed.

Parthenin is located in the trichomes (plant hairs) of the leaves and stems (Rodriguez et al 1976a). These are easily broken off, particularly when the plants are dry and brittle and, obviously this is one way for aerial dissemination of the sensitizer. In some ways Parthenium dermatitis resembles American ragweed (Ambrosia) dermatitis in having an airborne pattern of distribution. In the case of ragweed the allergenic determinant is in the oleoresin of the pollen (Hjorth et al 1976). Small amounts of parthenin are obtained in chloroform extracts of pollen of Parthenium hysterophorus (Mangala & Subba Rao, unpubl.) and, according to Ranade (1976), the pollen is responsible for the eczematoid dermatitis. As Parthenium pollen is sticky however, forming clumps in the flower heads, it may not be wind borne easily and this is one explanation for the relative unimportance of Parthenium pollen in hay fever or allergic rhinitis (Kahn & Grothaus 1936).

The weed has spread to nearly all the states of India and in cities such as Poona, Hubli and Banglalore, occupying vacant lots, ditches, roadsides, etc. According to a survey of the State Agriculture Department (Towers et al, in press), it occupies nearly one-third of the 122 km^2 of the city area of Bangalore. People in India come in direct contact with the plant in various ways: (a) working in fields, (b) using vacant lots as toilets, (c) using the dried plant as fuel, (d) clearing lots or gardens, or (e) uprooting it manually. There are no epidemics of eczematous dermatitis in Havana (Cuba), Kingston (Jamaica), Port-of-Spain (Trinidad), or many southern United States and Mexican towns where the weed is prolific and conspicuous (personal observations). This must be a reflection of the habits of the people; certainly it does not seem to be genetic because in a country such as Trinidad, where Parthenium is abundant and 40 to 50% of the population is of East Indian origin, there is a very low incidence of the allergy.

Parthenium hysterophorus not only has invaded food and fodder crop fields in India but even forest nurseries. In areas particularly heavily infested, buffaloes and goats may graze on the weed giving rise to the problem of 'bitter milk'. The weed has been shown to be quite toxic to buffaloes and cattle when fed at 5% level in fodder. Autopsies reveal necrosis and lesions of the liver and gastro-intestinal tract (Narasimham et al, unpubl.).

Public awareness of the problem has increased in India and a start has been made in eradication programs in the more badly affected parts of the country.

It should be borne in mind that compounds other than sesquiterpene lactones may be involved in some cases of allergic contact dermatitis. For instance pyrethrin II, an ester of chrysanthemumic acid, is a known sensitizer from Chrysanthemum spp (Burry et al 1973). Similarly, Tagetes minuta (Mexican marigold), a common weed in south eastern Africa, has a vesicant primary irritant effect on intact skin and can cause severe and prolonged contact dermatitis (Verhagen & Nyaga 1974). So far sesquiterpene lactones have not been found in the genus or even in other members of the tribe, Tageteae (Rodriguez 1975).

Parthenium dermatitis bears a marked resemblance to photodermatitis (A. Lonkar in litt) which is caused by exposure to sunlight. It is well known that allergic contact dermatitis caused by Compositae is hard to distinguish from phytophotodermatitis (Curwen & Jilson 1960). For example, ragweed (Ambrosia) dermatitis has been misdiagnosed as a photo-dermatitis (Hjorth 1976). Is there any relation between allergic contact dermatitis and photodermatitis evoked by Compositae? We believe that there may well be in some instances and that more careful studies are needed. This leads to a discussion of photoactive chemicals in the Compositae.

There exists a number of types of compounds in plants which damage human skin in the presence of light, the best known of these being the linear furanocoumarins of the Apiaceae, Rutaceae, Papilionaceae and Moraceae (Pathak et al 1974). In sunlight or artificial sources of long wave ultra-violet light (360-370 nm) these compounds cause cell damage and current hypothesis involves covalent cross-linking between double stranded DNA and the furanocoumarin in photochemical reactions (Musajo et al 1974).

Furanocoumarins or psoralens are not only phototoxic to human skin but also to bacteria and fungi (Daniels 1965; Fowlks et al 1958). A chance discovery by Daniels (1965), a dermatologist, that the achenes of the garden marigold (Tagete) contain a chemical or chemicals phototoxic to the yeast, Candida albicans, led us to a phytochemical investigation of Tagetes for the active substance or substances. Two of the phototoxic compounds isolated from Tagetes patula were identified (Chan et al 1975) as the thiophene derivatives, α-terthienyl and 5-(3-buten-1-ynyl)-2,2'-bithienyl (Fig 1), compounds which had been shown previously to be phototoxic to the nematode, Pratylenchus penetrans (Gommers & Geerligs 1973).

Our study was extended to 80 other species of Compositae (Camm et al 1975), and more recently to nearly 300 North, Central and South American species (Towers et al, 1977). Leaves, stems, roots and achenes of each species were assayed separately using Candida albicans as test organism. There was excellent correlation between occurrences of certain polyacetylenes and their thiophene derivatives and phototoxic activity. The activity, usually restricted to stem, root or achene, was sometimes even restricted to the pappus of the achene as in Tagetes. Activity was correlated with the occurrence of compounds such as the tridecapentaynene [$CH_3 - (C \equiv C)_5 - CH = CH_2$], or esters of matricarionol [$CH_3 - CH = CH - (C \equiv C)_2 - CH = CH - CH_2OCOR$]. These compounds themselves as well as a number of other polyacetylenes and thiophene compounds were shown to be active. Carbonyl compounds conjugated with a double bond and further conjugated with triple bonds are phototoxic. Where this conjugation is lacking the compounds are

inactive. It is possible that the mode of action of the polyacetylenes is similar to that of the furanocoumarins, ie, a light-mediated cross-linking of double-stranded DNA, requiring two reactive sites in a given polyacetylene molecule. However, this remains to be studied.

We have found recently that α-terthienyl can evoke photodermatitis in human skin (Chan et al, 1977). Thus, burning pain and erythema developed within 20 min of long wave UV-irradiation of α-terthienyl skin sites in contrast to 8-methoxypsoralen-evoked photodermatitis which developed at about 4 h. α-Terthienyl and related thiophenes occur in many Compositae particularly in the Tribes Helenieae, Heliantheae and Tageteae. In Tagetes the highest concentrations are in the roots but it is also in the flower heads (Glushka et al, unpubl).

Tagetes minuta, as mentioned previously, is an adventive weed in East Africa and, apart from its other undesirable properties, causes severe irritation and edema of small wounds such as scratches (Verhagen & Nyaga 1974). Walking through a field of marigolds on a sunny afternoon could, therefore, be a hazard. I found that the exposure of an area of the forearm, which had been treated with 1% solution of α-terthienyl in petrolatum, resulted in severe erythema within a few minutes in the tropical sun and to hyperpigmentation which persisted after 6 mo.

So far polyacetylenes such as Ø - $(C \equiv C)_3$ - CH_3 or CH_3 $(C \equiv C)$ - $CH = CH_2$, which we have established as being phototoxic to Candida and to certain pathogenic bacteria, have not been tested on human skin. It is more than likely that they have an effect and this could be important, particularly if these compounds are carried in pollen. Many Compositae contain polyacetylenes (Bohlmann et al 1973) as well as sesquiterpene lactones, and thus they may be capable of a dual 'attack' on exposed skin. The possibility of photodermatitis from Compositae is worth investigating, especially in those cases where eczematoid dermatitis bears a close resemblance to photo-dermatitis and where the offending species is known to contain reactive sesquiterpene lactones as well as photoactive polyacetylenes.

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