THE PRESENTLY KNOWN DISTRIBUTION OF FUROCOUMARINS (PSORALENS) IN PLANTS*

M. A. PATHAK, Ph.D.**, FARRINGTON DANIELS, Jr., M.D.*** and T. B. FITZPATRICK, M.D.**

The recent use of psoralen compounds (1) in the treatment of vitiligo and as a means of increasing the tolerance of human skin to solar radiation and increasing the pigmentation which follows exposure to ultraviolet radiation illustrates how ancient medical lore may sometimes be modified to satisfy present-day demands. The furocoumarins, more commonly known as psoralens, are pharmacologic agents which, with modern technics, can be isolated from herbal remedies that have been employed for many centuries (2). Concomitantly with recent progress in the synthesis of new organic molecules for therapeutic purposes, interest in many ancient drugs and herbal concoctions has been revived because some of these medicaments have been found to contain specific pharmacological agents which exert scientifically recognizable therapeutic effects.

Furocoumarins (psoralen, 8-methoxypsoralen (xanthotoxin) and 5-methoxypsoralen (bergapten)) occur naturally in the leaves, roots and fruit of plants which have been used for centuries in India, Egypt and other oriental countries (2) for the treatment of vitiligo. Fowlks *et al.* (3) have reported that furocoumarins exert a photosensitizing effect on bacteria in the presence of long-wave ultraviolet light. In a later publication, Fowlks (4) has also pointed out that these compounds belong to a group of substances which can inhibit certain aspects of plant growth without otherwise harming the plant; he has further postulated that furocoumarins may act as natural growth regulators in certain plants (5, 6). Chakraborty *et al.* (7) have shown that the psoralens (including psoralen and imperatorin) were the most effective antifungal agents among seventeen natural coumarin derivatives tested. Some hitherto unreported results of Dolcher, Rodighiero and Caporale have been mentioned by Musajo (8): they described the mutagenic properties of five furocoumarins and found 5-methoxypsoralen and psoralen to be almost as effective mutagenic agents as is light-sensitized trypaflavin. Altenburg (9) reports that psoralens increase the mutation rate in drosophila.

During the last three decades an increasing number of reports have been published about a form of dermatitis in man which follows contact with many plants and subsequent exposure of the skin to sunlight (10, 11, 12, 13). It has long been known that photosensitization dermatitis with residual pigmentation develops in skin which has come into contact with figs, cow parsnip, wild parsnip, wild carrot, fennel, caraway, anise, coriander, angelica, parsley and several other plants. The condition has also been described in individuals exposed to the oil of Persian limes (14) and among carrot processers (13, 15). Recently the phytophotodermatitis due to furocoumarins has become a public health problem among celery pickers (16). This phytophotodermatitis, as well as that which follows contact with plants of other species, is thought to be caused largely by furocoumarin compounds which are characteristically present in these plants. The occurrence of furocoumarins in many familiar edible plants, and the widely recognized photosensitizing action of these compounds have recently led the authors (17) to study the mechanisms of photosensitivity and photodynamic action in detail. Whether the skin can be photosensitized by ingestion of natural furocoumarin containing foods has not yet been established.

Several clinical manifestations of phytophotodermatitis have specific names: *e.g.*, "berloque dermatitis" which is the reaction to 5-methoxypsoralen present in the oil of Bergamot used in certain perfumes (10, 18, 19, 20); and "dermatitis bullosa striata pratensis" (21, 22, 23, 24) which follows exposure of the skin to sunlight after it has come into contact with "meadow grass" (in most cases *Agrimony eupatoria*).

Several publications dealing with dermatitis caused by plants and eau de cologne have appeared in European and American dermatologic journals. A large number of these deal with the erythemal response and hyperpigmentation associated with sea bathing and outdoor sun bathing on clear sunny days after the application of eau de cologne. It is known that several perfumes

* From the Research Laboratories of the Department of Dermatology of the Harvard Medical School at the Massachusetts General Hospital, Boston 14, Massachusetts and the Department of Dermatology of the University of Oregon Medical School, Portland, Oregon.

** Present address; Dept. of Dermatology Mass. General Hospital, Boston 14, Mass.

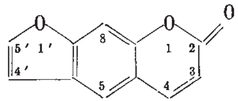
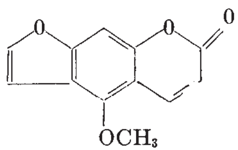
*** Present address: Division of Dermatology Cornell University Medical School, New York, N.Y.

This work was supported by Grant #CY-2837 (C-2 and C-3) P. E. T., and Grant #CY-5003 (C-1) from the National Institutes of Health, United States Public Health Service.

Received for publication November 24, 1961.

TABLE 1

Distribution of Furocoumarins in Nature

No.	Compound and Structure	Natural Sources	Common Name	Family	References
1.	Psoralen (Ficusin) 	Psoralea corylifolia	Babachi	Leguminosae	27, 28, 29
		Ficus carica	Fig	Moraceae	28, 30, 31
		Coronilla glauca		Leguminosae	8, 32
		Phebalium argenteum			33, 34
		Xanthoxylum flavum	West Indian satin wood	Rutaceae	35
2.	5-Methoxypsoralen (Bergapten, Majudin, Heraclin) 	Ficus carica	Fig	Moraceae	8, 28, 30, 36, 37, 38, 39
		Fagara xanthoxyloides	Artar prickly ash	Rutaceae	28, 37, 40
		Skimmia laureola	Neera	Rutaceae	8, 28, 37, 41
		Citrus bergamia (Risso)	Bergemot oil	Rutaceae	8, 28, 37, 42
		Ruta graveolens	Rue	Rutaceae	8, 38, 39, 43, 44, 45
		Citrus limonum	Lemon	Rutaceae	38
		Citrus acida	Lime	Rutaceae	37, 46
		Fagara schinofolia		Rutaceae	47
		Ligusticum acutifolium		Umbelliferae	8, 28, 37
		Ligusticum acutilobum		Umbelliferae	48
		Heracleum sphondylium	Cow parsley European cow parsnip	Umbelliferae	8, 28, 37, 39, 49
		Heracleum giganteum		Umbelliferae	8, 37, 39
		Ammi majus Linn	Bishop's weed	Umbelliferae	50
		Heracleum nepalense		Umbelliferae	8, 39
		Seseli indicum	Hoegen celery	Umbelliferae	8, 26, 37, 39
		Pastinaca sativa	Garden parsnip	Umbelliferae	8, 39, 51
		Heracleum lanatum	Cow parsnip	Umbelliferae	52
		Angelica archangelica	Angelica, Engelwurz	Umbelliferae	53, 54
		Ammi majus	Bishop's weed	Umbelliferae	39, 50
		Pimpinella magna		Umbelliferae	8, 39
		Pimpinella saxifraga	Cow parsnip	Umbelliferae	8, 28, 37, 39, 55, 56
		Petroselium sativum	Garden parsley	Umbelliferae	8, 39, 57

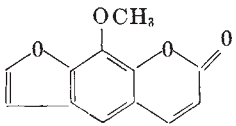
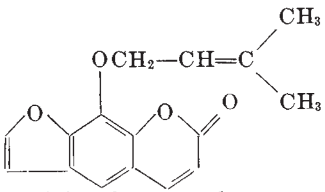
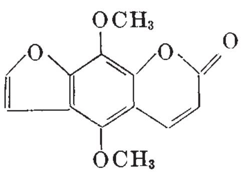
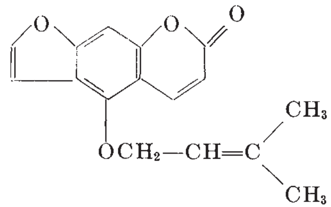
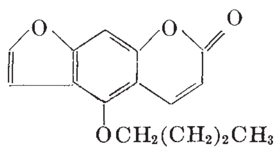
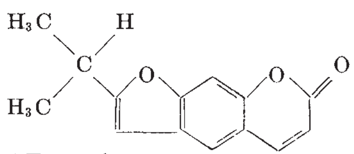
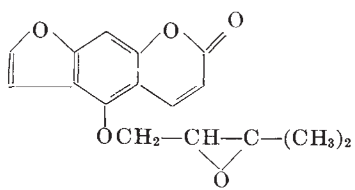
3. 8-Methoxypsoralen (Xanthotoxin or Methoxalen or Ammoidin) 	Ammi majus	Bishop's weed	Umbelliferae	50, 58, 59, 60, 61
	Angelica archangelica	Engelwurz	Umbelliferae	52
	Pastinaca sativa	Garden parsnip	Umbelliferae	51
	Ficus carica	Fig	Moraceae	38
	Ruta chalepensis		Rutaceae	8, 28, 37, 39, 41
	Fagara xanthoxyloides		Rutaceae	28, 29, 40, 62
	Ruta montana		Rutaceae	8, 39, 63
	Aegle marmelos	Bel	Rutaceae	64
	Ruta graveolens	Rue	Rutaceae	8, 38, 39, 44
	Luvanga scandens	Lavanga	Rutaceae	65
	Xanthoxylum flavum	West Indian satin wood	Rutaceae	35
	Ruta bracteosa		Rutaceae	41
4. 8-Isopentenyloxypsoralen (Imperatorin or Ammidin) 	Imperatoria ostruthium	Masterwort	Umbelliferae	28, 37, 66
		Hog fennel		
	Angelica glabra		Umbelliferae	28, 37, 64
	Angelica archangelica	Engelwurz	Umbelliferae	28, 37, 67
	Ammi majus		Umbelliferae	59, 60, 61
	Peucedanum ostruthium	Masterwort	Umbelliferae	28, 29
	Pastinaca sativa	Parsnip	Umbelliferae	37
	Prangos pabularia		Umbelliferae	37, 76
	Aegle marmelos	Bel	Rutaceae	37, 68, 69
	Ruta chalepensis		Rutaceae	53
5. 5,8-Dimethoxypsoralen (Isopimpinellin) 	Pimpinella saxifraga	Cow parsnip	Umbelliferae	28, 37, 70, 71
	Heracleum sphondylium	Cow parsley	Umbelliferae	28, 37, 72
	Sesli indicum	Hog celery	Umbelliferae	28, 37
	Skimmia laureola	Neera	Rutaceae	41
	Citrus aurantifolia	West Indian lime oil	Rutaceae	37, 73
	Luvanga scandens		Rutaceae	65
	Thamnosma montana		Rutaceae	5
	Fagara oilanthoides		Rutaceae	74
	Heracleum lanatum (var. nipponicum)		Rutaceae	52
	Citrus acida	Lime	Rutaceae	46

TABLE 1—*Continued*

No.	Compound and Structure	Natural Sources	Common Name	Family	References
6.	5-Isopentenyloxypsoralen (Isoimperatorin)	Peucedanum ostruthium	Masterwort	Umbelliferae	28, 29, 37
		Imperatoria ostruthium	Masterwort	Umbelliferae	28
		Pastinaca sativa	Garden parsnip	Umbelliferae	75
					
7.	Prangenine	Prangos pabularia		Umbelliferae	76
					
8.	4′-Methoxy,-5′-isopropylpsoralen (Peucedanin)	Peucedanum officinale	Masterwort	Umbelliferae	28, 77
		Prangos pabularia		Umbelliferae	37
					
9.	5-Epoxy isopentenyloxypsoralen (Oxypeucedanin)	Peucedanum officinale	Masterwort	Umbelliferae	28, 29, 37
		Peucedanum ostruthium	Masterwort	Umbelliferae	37
		Prangos pabularia		Umbelliferae	37
		Imperatoria ostruthium	Masterwort	Umbelliferae	8
					

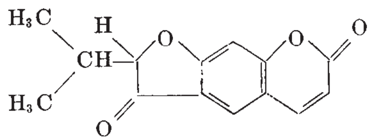
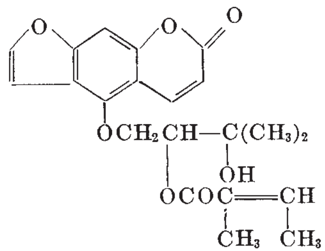
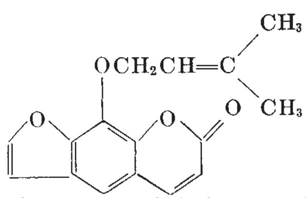
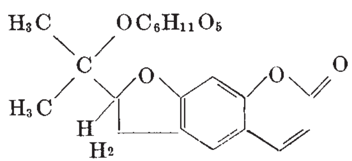
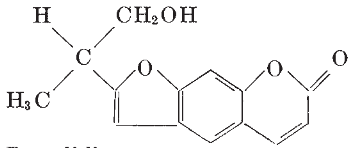
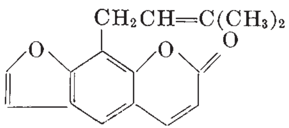
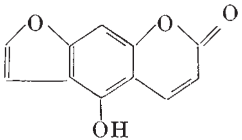
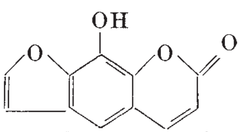
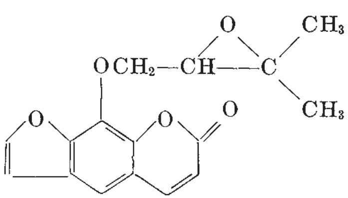
10. Oreoselone	Peucedanum officinale Peucedanum oreoselinum	Masterwort	Umbelliferae	29 78
				
11. Ostruthol	Peucedanum ostruthium	Masterwort	Umbelliferae	28, 29, 37, 79
				
12. 5-Methoxy,8-isopentenyloxypsoralen (Phellaptorin)	Angelica glabra Phellopterus littoralis		Umbelliferae Umbelliferae	29 29
				
13. 4′,5-dihydro,5′(-l-glucosoxy-isopropyl) psoralen (Nodakenin)	Peucedanum decursivum		Umbelliferae	37, 80
				

TABLE 1—*Continued*

No.	Compound and Structure	Natural Sources	Common Name	Family	References
14.	Aglucone of nodakenin (Nodakenetin) 	Peucedanum decursivum	Marmesin	Umbelliferae	37, 80, 81, 82
15.	Psoralidin 	Psoralea corylifolia	Bavachi	Leguminosae	83
16.	5-Hydroxypsoralen (Bergaptol) 	Citrus bergamia (Risso) Citrus aurantifolia	Bergamot oil West Indian lime oil	Rutaceae Rutaceae	28, 29 37, 42, 73
17.	8-Hydroxypsoralen (Xanthotoxol) 	Angelica archangelica	Engelwurz	Umbelliferae	28, 29, 37, 67
18.	5-Methoxy-8-epoxyisopentenyloxypsoralen (Byak angelicol) 	Angelica glabra	Byakusi (Japanese ivy)	Umbelliferae	37

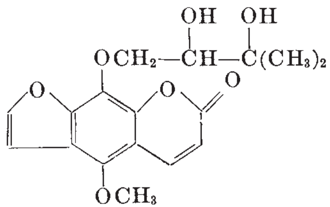
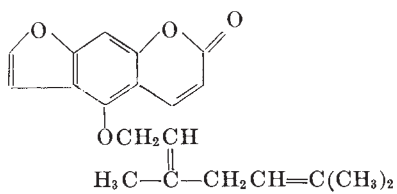
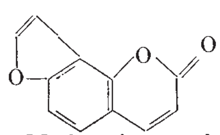
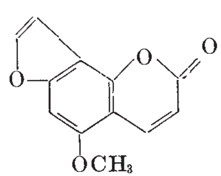
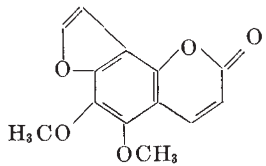
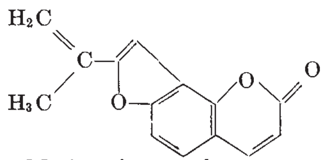
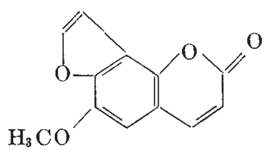
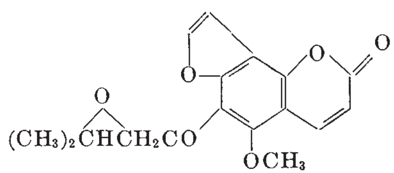
19. 5-Methoxy-8-(2,3-dihydroxy)-isopentyloxypsoralen (Byak angelicin) 	Angelica glabra	Byakusi (Japanese ivy)	Umbelliferae	37
20. 5-Geranyloxypsoralen (Bergamotin) 	Citrus aurantifolia	Bergamot oil Persian lime	Rutaceae	28, 33, 37
21. Isopsoralen (Angelecin) 	Psoralea corylifolia Angelica glabra	Bavachi	Leguminosae Umbelliferae	37, 84, 85 37, 52, 86
22. 5-Methoxyisopsoralen (Isobergapten) 	Pimpinella saxifraga Heracleum sphondylium Heracleum lanatum Pimpinella magna	Cow parsnip Bibernell Cow parsnip	Umbelliferae Umbelliferae Umbelliferae Umbelliferae	28, 37, 71, 80 28, 37, 70, 71, 72 52 8

TABLE 1—*Concluded*

No.	Compound and Structure	Natural Sources	Common Name	Family	References
23.	5,-6-Dimethoxyisopsoralen (Pimpinellin)	Pimpinella saxifraga	Cow parsnip	Umbelliferae	28, 37, 70
		Heracleum sphondylium	Cow parsley	Umbelliferae	28, 37
		Pimpinella magna		Umbelliferae	8
		Heracleum lanatum		Umbelliferae	52
					
24.	Oroselon	Peucedanum oreoselinum		Umbelliferae	78, 87
					
25.	6-Methoxyisopsoralen (Sphondin)	Pimpinella saxifraga	Cow parsnip	Umbelliferae	55, 56
		Heracleum sphondylium		Umbelliferae	28, 29, 72
		Thamnosma montana		Rutaceae	5
		Heracleum lanatum		Rutaceae	52
					
26.	Thamnosmin	Thamnosma montana		Rutaceae	5
					

27. 4′,5′-Dihydro-5′-(1-hydroxyisopropyl),4′-hydroxy-diisovaleryl ester (Athamentin)	Athamanta oreoselinum	Umbelliferae	87
	Peucedanum oreoselinum	Umbelliferae	29, 87

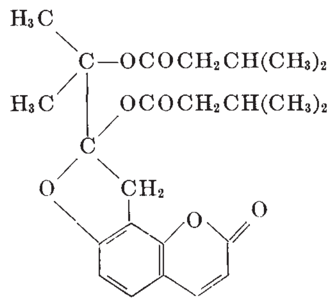


TABLE 2

Plants Reported to Evoke Phytophotodermatitis

Common Name	Botanical Name	Natural Order	References
Fig	Ficus carica	Moraceae	10, 26
Parsnip	Pastinaca sativa	Umbelliferae	21, 22, 88, 89
Cow parsnip	Heracleum sphondylium	Umbelliferae	10, 25, 90
Garden parsnip	Heracleum gigantum	Umbelliferae	13, 91, 92
Wild parsnip	Pastinaca sativa	Umbelliferae	
	Heracleum mantegazzianum		
Fennel	Foeniculum vulgare	Umbelliferae	10, 13
Dill	Anethum graveolens	Umbelliferae	10, 11, 13
Parsley	Peucedanum oreoselium	Umbelliferae	10, 11, 13
Wild carrot	Daucus carota	Umbelliferae	10, 11, 13
Garden carrot	Daucus sativa	Umbelliferae	15, 93
Masterwort	Peucedanum ostruthium	Umbelliferae	25
Celery	Apium graveolens	Umbelliferae	16, 88, 94
Atrillal	Ammi majus	Umbelliferae	95
Angelica	Angelica species	Umbelliferae	13
Common rue	Ruta graveolens	Rutaceae	10, 96
Gas plant	Dictamus albus	Rutaceae	97
Lime bergamot	Citrus bergamia	Rutaceae	10, 11, 13
	Dictamnus fraxinella	Rutaceae	10
Lime	Citrus aurantiom	Rutaceae	Rutaceae
Lime	Citrus aurantifolia	Rutaceae	10, 14
Persian lime (Tahitian, Bearss)	Citrus aurantifolia, var. Swingle	Rutaceae	10, 14
Buttercup	Renunculus species	Renunculaceae	10, 13
Mustard	Brassica species	Cruciferae	11, 13
	Sinapsis arevensis		98
Blind weed	Convolvulus arevensis	Convolvulaceae	10, 11, 92
Agrimony	Agrimony eupatoria	Rosaceae	10, 13
Yarrow (milfoil)	Achilleae millefolium	Compositae	10
Goose foot	Chenopodium species	Chenopodiaceae	11, 13, 99
Bavachi	Psoralea coryifolia	Leguminosae	25, 95
St. John's wort	Hypericum perforatum	Hypericaceae	13
	Hypericum concinnum		

contain fluorescent materials some of which are furocoumarins.

In 1942, Klaber (10) suggested the term "phytophotodermatitis" for the reaction to sunlight of skin which has been in contact with certain species of plants. He reviewed the evidence that wavelengths of ultraviolet radiation between 3,200 and 3,800 Å (0.32–0.38 micron) were required to initiate the reaction, and emphasized the futility of testing with mercury-arc lamps. He stated that, when a mercury-vapor lamp was employed, the reaction could only be demonstrated after filtration through windowglass. He reported that if the shorter ultraviolet rays were not thus filtered off, the erythema produced by these alone precluded a dose of the longer rays sufficient to excite the phytogenic reaction. This no doubt explains the failure of many observers to reproduce berloque dermatitis and other types of this reaction, when artificial sources of light were used. Klaber thus foretold experimental difficulties to be encountered years later.

The work of Kuske (25) merits review because it established the relationship between the chemical components of certain plant tissues and the development of phytophotodermatitis. Kuske reviewed the earlier proposal of Kitchevatz (26) that chlorophyll is the photosensitizer in exogenous percutaneous photosensitization; he also studied the latent period, the intensity and the residual effects of the reaction produced by fig extracts, and described the residual effects as intense, persisting pigmentation. In experiments with plant extracts, Kuske obtained mild erythema due to photosensitization reactions to *Pastinaca sativa*, *Ficus carica* and *Angelica officinalis*, and severe (blister formation) reactions to *Ruta graveolens* and *Heracleum manteaazzianum.*

He pointed out that the presence of certain chemical substances in plants tends to follow botanical classifications and that the Rutaceae, Umbelliferae and Moraceae are capable of evoking photosensitization reactions. With Dr. Mickelmann, Kuske identified the photosensitizing compounds of the furocoumarin group and studied the reaction of normal skin to solutions of bergapten (5-methoxypsoralen) and oxypeucedin. In his experiments, allergic factors were eliminated as causes of the reactions observed because the reactions occurred in all individuals.

This survey of the literature has been made in an attempt to determine how widespread the distribution of furocoumarins is in plants. Table 1 shows the distribution of these substances in plants, in so far as it has been reported in available publications. A list of plants which are known to cause phytophotodermatitis constitutes Table 2. Existing data obviously do not indicate whether plants not mentioned in the literature were omitted from lists because they contain no furocoumarins or because their chemical components have not been identified. Table 1 lists the more common of the psoralen derivatives, the botanical, and in some cases the common name of the plants in which they occur, the family to which these plants belong and the sources from which the data were obtained. Table 2 is a list of plants that have been reported to induce phytophotodermatitis. As can be seen, about 50 per cent of these belong to the order Umbelliferae. Next most numerous are the Rutaceae. Single members of the Moraceae, Renunculaceae, Cruciferae, etc. are also included. No claim is made that the listing in either table is complete.

Discussion

As can be seen in Table 1, only four or five major plant families have been found to contain furocoumarins. The Umbelliferae and Rutaceae are the largest and most important of these; the Leguminosae and Moraceae include few but widely distributed species. Geissman and Hinreiner (37) have proposed a mechanism of biogenesis of furocoumarins in the various plant species and have suggested that they owe their formation to biochemical processes which characteristically occur only in certain genera and families. It is not surprising, therefore, that furocoumarins seem to be present in plants which belong only to a few plant families.

The furocoumarins listed in Table 1 were extracted from various parts of the plant, *e.g.*, leaves, seeds, fruits, roots and rhizomes. These compounds are most abundant in plants which have flowered and in ripe seeds and fruits; during the early stages of plant growth their presence is not easily recognizable.

Various investigators have studied the photosensitizing action of many naturally occurring furocoumarins and their synthetically prepared derivatives in human skin, guinea-pig skin and bacteria (3, 8, 100, 101, 102, 103). Not all of the naturally occurring furocoumarins tested were found to produce photosensitization. When applied topically, imperatorin, isopimpinellin, oxypeucedanin, bergaptol, xanthotoxol, angelecin, isobergapten and pimpinellin do not induce erythema. Psoralen, xanthotoxin, bergapten, isoimperatorin and bergamotin, on the other hand, have been found to be biologically active. Many others still remain to be tested, *e.g.*, prangenine, peucedanin, sphondin, oreoselone, nodakenetin, psoralidin, phellaptorin, nodakenin, oroselon, thamnosmin, byak angelicol, byak angelicin, athamentin, etc.

The data presented in Table 2 show that members of Umbelliferae are outstanding in causing photosensitization contact dermatitis. Contact with wild carrots, fennel, caraway, anise, corriander, celery, angelica species, wild parsnip, parsley and several other plants is well known to cause photosensitization (10, 11, 12, 13). The members of the Rutaceae also frequently induce phytophotodermatitis. They include the common rue, gas plant, and several varieties of lime and other citrus fruits, and bergamot. In the Moraceae family the fig has been known for a long time to have a photosensitizing action. Other botanical families associated with photosensitization are Convolvulaceae, Compositae, Cruciferae, Rosaceae and Renunculaceae.

The etiology of this phytophotosensitization has not been established. One thing is clear, *i.e.*, that light, particularly in the region of 3200–3800 Å, plays an important part (14, 92, 104). The observations related to the action spectrum of 8-methoxypsoralen which have been reported by Buck *et al.* (105) and Pathak (104) indicate that the wavelengths which most effectively evoke the erythemal photosensitization response are in the range between 340 and 380 mμ, with maximum effectiveness at 360 mμ. Various plant species reported to cause photosensitization (Table 2) have been analyzed by several workers and shown to contain furocoumarins, especially xanthotoxin, bergapten, psoralen, etc. These compounds are highly photosensitizing and cause dermatitis and residual pigmentation. It is therefore not surprising that several species of Umbelliferae, Rutaceae, etc. have been implicated in phytophotodermatitis. It is possible that other plants which have not yet been analyzed may constain active furocoumarins and could become the major causes of skin sensitization in the presence of light, giving rise to erythema and subsequent residual pigmentation.

SUMMARY

In this review, we have attempted to outline the distribution of photosensitizing furocoumarins in the plant kingdom. Available data indicate that they are found in the orders Umbelliferae, Rutaceae, Moraceae and Leguminosae. Various plants implicated in the causation of photosensitization dermatitis (phytophotodermatitis) belong to the orders Umbelliferae and Rutaceae. It is likely that photosensitization contact dermatitis is due largely, if not entirely, to the action of photosensitizing compounds related to furocoumarins. The distribution of furocoumarins in plants is probably far more widespread than the reported incidence of phytophotodermatitis would lead one to suppose. For the initiation of phytophotodermatitis, there are two requisites: 1) contact with a sensitizing furocoumarin and 2) subsequent exposure to ultraviolet radiation of wavelengths greater than 3200 Å (usually sunlight). It is to be anticipated that more specific varieties of phytophotodermatitis will be recognized as more photosensitizing compounds are identified.

REFERENCES

1. Symposium: Psoralens and radiant energy. *Suppl., J. Invest. Derm.*, **32,** *Part II*: 132–391, 1959.
2. Fitzpatrick, T. B. and Pathak, M. A.: Historical aspects of methoxsalen and other furocoumarins. *J. Invest. Derm.*, **32,** *Part II*: 229, 1959.
3. Fowlks, W. L., Griffith, D. G. and Oginsky, E. L.: Photosensitization of bacteria by furocoumarins and related compounds. *Nature*, **181:** 571, 1958.
4. Fowlks, W. L.: The chemistry of the psoralens. *J. Invest. Derm.*, **32,** *Part II*: 249, 1959.
5. Bennett, E. L. and Bonner, J.: Isolation of plant growth inhibitors from *Thamnosma montana*. *Amer. J. Botany*, **40:** 29, 1953; also, personal communication.
6. Rodighiero, G.: Influenza di furocumarine naturali sulla germinazione dei semi e sullo sviluppo dei germogli e delle radici di latuga. *G. di Biochim.*, **3:** 138, 1954.
7. Chakraborty, D. P., Das Gupta, A. and Bose, P. K.: On the antifungal action of some natural coumarins. *Ann. Biochem. Exp. Med.*, **17:** 57, 1957.
8. Musajo, L.: Interessanti proprieta delle furocumarine naturali. *Il Farmaco, Ed. Sci.*, **10:** 1, 1955.
9. Altenburg, E.: Studies on the enhancement of the mutation rate by carcinogens. *Texas Rep. Biol. Med.*, **14:** 481, 1956.
10. Klaber, R.: Phyto-photo-dermatitis. *Brit. J. Derm.*, **54:** 193, 1942.
11. Bellringer, H. E.: Phyto-photo-dermatitis. *Brit. Med. J.*, **1:** 984, 1949.
12. Goldsmith, W. N. and Hellier, F. F.: *Recent Advances in Dermatology*, second edition. New York, Blakiston Company, Inc., 1954.
13. Klauder, J. V. and Kimmich, J. M.: Sensitization dermatitis to carrots. *A.M.A. Arch. Derm.*, **74:** 149, 1956.
14. Sams, W. M.: Photodynamic action of lime oil (Citrus aurantifolia). *A.M.A. Arch. Derm.*, **44:** 571, 1941.
15. Peck, S. M., Spolyer, L. W. and Mason, H. S.: Dermatitis due to carrots. *Arch. Derm. Syph.*, **49:** 266, 1944.
16. Birmingham, D. J., Key, M. M., Tubich, G. E. and Perone, V. B.: Phototoxic bullae among celery harvesters. *A.M.A. Arch. Derm.*, **83:** 73, 1961.
17. Pathak, M. A., Allen, B., Fellman, J. H. and Ingram, D. J. E.: Photosensitization and the effect of ultraviolet radiation on the production of unpaired electrons in the presence of furocoumarins (psoralens). *Biochim. et Biophys. Acta*, **54:** 506, 1961.
18. Gross, P. and Robinson, L. B.: Berlock dermatitis, unusual dermatitis and pigmentation following use of perfume. *Arch. Derm. Syph.*, **21:** 637, 1930.
19. Goodman, H.: Perfume dermatitis. *Brit. J. Derm.*, **43:** 177, 1931.
20. Szántó, J.: Pigmentationen der Haut, entstanden durch die sensibilisierende Wirkung aromatischer Öle. *Derm. Wschr.*, **45:** 1820, 1929.
21. Oppenheim, M.: Dermatite bulleuse striée consécutive aux bains de soleil dans les pres (dermatitis bullosa striata pratensis). *Ann. Derm. Syph.*, **3:** 1, 1932.
22. Oppenheim, M.: Dermatitis striata pratensis bullosa (grass or meadow dermatitis). *Arch. Derm. Syph.*, **46:** 541, 1942.
23. O'Donnovan, W. J.: Dermatitis bullosa striata pratensis. Agrimony dermatitis. *Brit. J. Derm.*, **54:** 39, 1942.
24. Lee, H. G.: Dermatitis bullosa striata pratensis. *Proc. Roy. Soc. Med.*, **40:** 14, 1946.
25. Kuske, H.: Experimentelle Untersuchungen zur Photosensibilisierung der Haut durch pflanzliche Wirkstoffe; Lichtsensibilisierung durch Furocumarine als Ursache verschiedener phytogener Dermatosen. *Arch. Derm. u. Syph.*, **178:** 112, 1938; Perkutane Photosensibilisierung durch pflanzliche Wirkstoffe. *Dermatologica*, **82:** 273, 1940.
26. Kitchevatz, M.: Etiologie et pathogènèse de la dermatite des figues. *Bull. Soc. Franc. Derm. Syph.*, **41:** 1751, 1934; Nouvelles recherches sur la photosensi-

bilisation de la peau. *Bull. Soc. Franc. Derm. Syph.*, **43:** 581, 1936.
27. JOIS, H. S., MANJUNATH, B. L. AND VENKATA RAO, S.: Chemische Untersuchung der Samen von Psoralea corylifolia, Linn. I. *Chem. Zentr.*, **104** (*II*): 77, 1933; Chemical examination of seeds of Psoralea corylifolia. *J. Indian Chem. Soc.*, **10:** 41, 1933.
28. SPÄTH, E.: Die natürlichen Cumarine. *Ber. Deut. Chem. Ges.*, **70 A:** 83, 1937.
29. SETHNA, S. M., AND SHAH, N. M.: The chemistry of coumarins. *Chem. Rev.*, **36:** 1, 1945.
30. OKAHARA, K.: The constituents of the leaves of Ficus carica. *Bull. Chem. Soc., Japan*, **11:** 389, 1936; *Brit. Chem. Abstr.*, 1121, 1936.
31. SPÄTH, E., OKAHARA, K. AND KUFFNER, F.: Die Identität von Ficusin mit Psoralen. *Ber. Deut. Chem. Ges.*, **70**(*I*): 73, 1937.
32. STOLL, A., PEREIRA, A. AND RENTZ, J.: Das Furocoumarin und die β-D-Glucosido-furocoumarinsäure aus den Samen von Coronilla-Arten. *Helv. Chim. Acta*, **33:** 1637, 1950.
33. BOSE, P. K. AND FINLAYSON, H. H.: Occurrence of psoralen in Phebalium argenteum. *J. Indian Chem. Soc.*, **15:** 516, 1938.
34. FINLAYSON, H. H.: Essential oil of Phebalium argenteum Smith. *Trans. Roy. Soc., S. Australia*, **52:** 235, 1928.
35. KING, F. E., HOUSLEY, J. R. AND KING, T. J.: Coumarin constituents of Fagara macrophylla, Zanthoxylum flavum and chloroxylon swietenia. *J. Chem. Soc., Part II*, 1392, 1954.
36. SPÄTH, E. AND HILLEL, R.: Zur Kenntnis des Psoralens und der Elektroreduktion des Naphthalimids. Bemerkungen zur Arbeiten von Kunio Okahara und Buhei Sakurai. *Ber. Deut. Chem. Ges.*, **72 B:** 1577, 1939.
37. GEISSMAN, T. A. AND HINREINER, E.: Theories of the biogenesis of flavanoid compounds. *Botanical Reviews*, **18:** 77, 1952.
38. RODIGHIERO, G., CAPORALE, G. AND RAGAZZI, E.: Ricerche sulle cumarine presenti nella Ruta graveolens, nelle foglie di Ficus carica e nell'essenza di Citrus limonum. *Atti Instituto Veneto Sci. Lett. e Arti*, **111:** 125, 1953.
39. MUSAJO, L., RODIGHIERO, G. AND CAPORALE, G.: The photodynamic activity of natural coumarins. *Bull. Soc. Chim. Biol.*, **36:** 1213, 1954. (French)
40. THOMS, H.: Ueber die Konstitution des Xanthotoxins und seine Beziehungen zum Bergapten. *Ber. Deut. Chem. Ges.*, **44:** 3325, 1911; The chemical constituents of the fruits of Fagara xanthoxyloides, Lam. *Pharm. J., Berlin*, **88:** 29, 1911–12. (German)
41. CHATTERJEE, A. AND BHATTACHARYA, A.: The active principles of Skimmia laureola. *J. Indian Chem. Soc.*, **30:** 33, 1953.
42. MULDER, G. J.: Stearopten des Bergamottols: Ueber die Zusammensetzung einiger Stearopten und ätherischen Oele. *Ann. der Pharm.*, **31:** 67, 1839.
43. BRANDT, W.: Zur Anatomie und Chemie der Ruta graveolens L. *Arbeiten Pharm. int. Univers*, Berlin, **11:** 82, 1914; *Chem. Zentr.*, **86**[2](*II*); 1199, 1915.
44. RODIGHIERO, G., CAPORALE, G. AND ALBIERO, G.: Ricerche sulle cumarine della Ruta graveolens. *Gazz. Chim. Ital.*, **84:** 874, 1954.
45. MUHLEMANN, H.: Coumarin like constituents of Herba rutae. *Pharm. Acta Helv.*, **13:** 45; 330, 1938.
46. KHASTAGIR, H.: Natural coumarins isolated from the leaves of Citrus acida. *J. Indian Chem. Soc.*, **24:** 421, 1947.
47. NAKAOKI, T. AND MORITA, N.: Constituents of the fruits of Fagara species of Japan. *J. Pharm. Soc., Japan*, **73:** 770, 1953.
48. KARIYONE, T. AND KANNO, M.: Constituents of the fruits of Ligusticum acutilobum, Sieb. et Zucc. I. *J. Pharm. Soc., Japan*, **56:** 662, 1936.
49. SPÄTH, E. AND RASCHAKA, S.: Heraclin. *Ber. Deut. Chem. Ges.*, **67B:** 62, 1934.
50. FAHMY, I. R. AND ABU-SHADY, H.: The isolation and properties of ammoidin, ammidin, and majudin and their effect in the treatment of leucodermia. *Quart. J. Pharm. & Pharmacol.*, **21:** 499, 1948.
51. KADIR, E. A. E.: *Pastinaca sativa* (*Linné*). M.S. Thesis, Cairo University, 1954.
52. FUJITA, M. AND FURUYA, T.: Pharmacognostic study of crude drugs containing coumarins and their derivatives. *J. Pharm. Soc., Japan*, **76** (*5*): 535, 1956.
53. WEHMER, C.: Angelica archangelica L., Engelwurz, Archangelica officinalis Hoffm., A. officinalis Mnch. In *Die Pflanzenstoffe: Botanisch-Systematisch Bearbeitet, Bestandteile und Zusammensetzung der einzelnen Pflanzen und deren Produkte. Second edition, Vol. II*, 887. Jena, Gustav Fischer, 1929.
54. SPÄTH, E. AND VIERHAPPER, F.: Natural coumarins. XL. Coumarins of the drug Samen angelicae. *Monatsch. Chem.*, **72:** 179, 1938. (German)
55. WESSELY, F. AND NEUGEBAUER, L.: Contents of the root of Pimpinella saxifraga. *Monatsch. Chem.*, **84:** 217, 1953. (German)
56. WESSELY, F. AND KOTLAN, J.: Photodimerization of furocoumarins; sphondylin. *Monatsch. Chem.*, **86:** 430, 1955. (German)
57. MUSAJO, L., CAPORALE, G. AND RODIGHIERO, G.: Isolamento del bergaptene del sedano e del prezzemolo. *Gazz. Chim. Ital.*, **84:** 870, 1954.
58. FAHMY, I. R. AND ABU-SHADY, H.: Ammi majus (Linné): pharmacognostical study and isolation of a crystalline principle ammoidin. *Quart. J. Pharm. & Pharmacol.*, **20:** 281, 1947.
59. FAHMY, I. R., ABU-SHADY, H., SCHÖNBERG, A. AND SINA, A.: A crystalline principle from Ammi majus (Linné). *Nature*, **160:** 468, 1947.
60. SCHÖNBERG, A. AND SINA, A.: Xanthotoxin from fruits of Ammi majus (Linné). *Nature*, **161:** 481, 1948.
61. SCHÖNBERG, A. AND SINA, A.: Experiments with xanthotoxin and imperatorin obtained from fruits of Ammi majus (Linné). *J. Amer. Chem. Soc.*, **72:** 1611; 3396; 4826, 1950.
62. PRIESS, H.: Constituents of Fagara xanthoxyloides. *Ber. Deut. Pharm. Ges.*, **21:** 267, 1910. (German)
63. PFAU, A. S.: Volatile plant constituents, IX. Certain unpublished constituents of essential oil of rue. *Helv. Chim. Acta*, **22:** 382, 1939.

64. Mukerji, B.: Psoralea and other indigenous drugs used in leucoderma. *J. Sci. Indust. Res.*, **15 A**: 1, 1956.
65. Bose, P. K. and Mookerjee, A.: On the constitution of natural coumarins isolated from Luvanga scandens (Lam). *J. Indian Chem. Soc.*, **21**: 181, 1944.
66. Späth, E. and Holzen, H.: Plant fish poisons. V. Constitution of imperatorin (from Imperatoria ostruthium). *Ber. Deut. Chem. Ges.*, **66 B**: 1137, 1933. (German)
67. Späth, E. and Vierhapper, F.: Natural coumarins. XXIII. Xanthotoxol, a new natural product from Semen angelicae, and the total synthesis of xanthotoxol and imperatorin. *Ber. Deut. Chem. Ges.*, **70 B**, 248, 1937. (German)
68. Späth, E., Bose, P. K., Gruber, W. and Guha, N. C.: Natural coumarins. XXVIII. Marmelosin. *Ber. Deut. Chem. Ges.*, **70** (*I*): 1021, 1937. (German)
69. Chatterjee, A. and Mitra, S. S.: Constitution of the active principles isolated from the matured bark of Aegle marmelos correa. *J. Amer. Chem. Soc.*, **71**: 606, 1949.
70. Wessely, F. and Kallab, F.: Constituents of the roots of Pimpinella saxifraga. *Monatsch. Chem.*, **59**: 161, 1932. (German)
71. Wessely, F. and Nadler, E.: Constituents of the roots of Pimpinella saxifraga, II. *Monatsch. Chem.*, **60**: 141, 1932. (German)
72. Späth, E. and Simon, A. F. J.: Natural coumarins. XVI. Coumarins of the roots of Heracleum sphondylium L. *Monatsch. Chem.*, **67**: 344, 1936. (German)
73. Caldwell, A. G. and Jones, E. R. H.: The constituents of expressed West Indian Lime oil. *J. Chem. Soc.*, *Part II*, 540, 1945.
74. Nakaoki, T. and Morita, N.: Constituents of the fruits of Fagara species of Japan. *J. Pharm. Soc., Japan*, **73**: 770, 1953.
75. Hakim, R. E.: *A contribution to the Galenical and pharmacological study of Ammi majus (Linné) and its constituents*. M.S. Thesis (Pharmacy), Cairo University, 1955.
76. Pigulevskii, G. V. and Kuznetsova, G. A.: Structure of furocoumarin, prangenine. *Zuhr. Obshchëi Khim.* **23**: 1237, 1953. (Russian)
77. Späth, E., Klager, K. and Schlösser, C.: Constitution of peucedanin and oreoselone. *Ber. Deut. Chem. Ges.*, **64 B**: 2203, 1931. (German)
78. Späth, E., Platzer, N. and Schmid, H.: Natural coumarins. LII. Constitution of oroselone. *Ber. Deut. Chem. Ges.*, **73 B**: 709, 1940. (German)
79. Späth, E. and Christiani, F.: Plant fish poisons. VII. Constitution of ostruthol (from Imperatoria ostruthium). *Ber. Deut. Chem. Ges.*, **66**: 1150, 1933. (German)
80. Späth, E. and Tyray, E.: Natural coumarins. L. Constitution of the nodakenin from Peucedanum decursivum Maxim. *Ber. Deut. Chem. Ges.*, **72 B**: 2089, 1939. (German)
81. Arima, J.: The constitution of nodakenin, a new glucoside from Peucedanum decursivum Maxim. I. *Bull. Chem. Soc., Japan* **4**: 16, 1929.
82. Späth, E. and Kainrath, P.: Die Konstitution des Nodakenins aus Peucedanum decursivum Maxim. *Ber. Deut. Chem. Ges.*, **69 B**, 2062, 1936. (German)
83. Chakravarti, K. K., Bose, A. K. and Siddiqui, S.: Chemical examination of seeds of Psoralea corylifolia. *J. Sci. Indust. Res.*, **7 B**, 24, 1948.
84. Jois, H. S. and Manjunath, B. L.: Identity of isopsoralen, a constituent of the seeds of Psoralea corylifolia L., with angelicin from the roots of Angelica archangelica L. *Ber. Deut. Chem. Ges.*, **69 B**: 964, 1936; *Proc. Indian Sci. Congr.*, **21**: 243, 1934. (German)
85. Jois, H. S. and Manjunath, B. L.: Ueber der Indentität von Iso-psoralen, (einem Bestandteil der Samen von Psoralea corylifolia L., mit Angelicin) aus den Wurzeln von Angelica archangelica L. *Ber. Deut. Chem. Ges.*, **69**: 964, 1936.
86. Späth, E. and Pesta, O.: Ueber natürliche cumarine. XI. Die Konstitution des Angelicins (aus Angelica archangelica L.). *Ber. Deut. Chem. Ges.*, **67**: 853, 1934.
87. Späth, E. and Schmid, H.: Natural coumarins. LIII. Constitution of athamantin. *Ber. Deut. Chem. Ges.*, **73**: 1309, 1940. (German)
88. Legrain, M. M. and Barthe, R.: Dermite professionelle des mains et des avant-bras chez un remasseur de celeris. *Bull. Soc. Franc. Derm. Syph.*, **33**: 662, 1926.
89. Straton, C. R.: Dermatitis venenata. *Brit. Med. J.*, **2**: 1139, 1912.
90. Miescher, G. and Burckhardt, W.: Herakleum dermatitis: case presentation, Swiss Dermatologic Association, Oct. 3–4, 1936. *Schweiz. Med. Wschr.*, **67**: 82, 1937. (German)
91. Belisario, J. C.: Parsnip dermatitis in the tropics under active service conditions. *Aust. J. Derm.*, **1**: 183, 1953.
92. Jensen, T. and Hansen, K. G.: Active spectral range for phytogenic photodermatosis produced by Pastinaca sativa (dermatitis bullosa striata pratensis, Oppenheim). *Arch. Derm. Syph.*, **40**: 566, 1939.
93. Vickers, H. R.: The carrot as a cause of dermatitis. *Brit. J. Derm.*, **53**: 52, 1941.
94. Henry, S. A.: Celery itch: dermatitis due to celery in vegetable canning. *Brit. J. Derm.*, **45**: 301, 1933; Further observations on dermatitis due to celery in vegetable canning. *Brit. J. Derm.*, **50**: 342, 1938.
95. Pathak, M. A.: Unpublished observations.
96. Szegö, L. and Dolinay, V.: Durch Ruta graveolens verursachte massenhafte Dermatitis bullosa als Berufurschädigung. *Derm. Wschr.*, **130** (*45*): 1180, 1954.
97. Cummer, C. L. and Dexter, R.: Dermatitis caused by Dictamnus albus (gas plant); example of photosensitization. *J. A. M. A.*, **109**: 495, 1937.
98. Spillman, L. and Weis, J.: Psoriasis généralizé et arthropathies. *Bull. Soc. Franc. Derm. Syph.*, **38**: 82, 1931.
99. Gryzbowski, M.: Peculiar, pellagra-like skin sensitization to light in starving persons. *Brit. J. Derm.*, **60**: 410, 1948.
100. Pathak, M. A. and Fitzpatrick, T. B.: Bioassay of natural and synthetic furocoumarins (psoralens). *J. Invest. Derm.*, **32**: 509, 1959.

101. Pathak, M. A., Fellman, J. H. and Kaufman, K. D.: The effect of structural alterations on the erythemal activity of furocoumarins: psoralens. *J. Invest. Derm.*, **35:** 165, 1960.

102. Musajo, L., Rodighiero, G. and Caporale, G.: L'activité photodynamique des coumarines naturelles. *Bull. Soc. Chim. Biol.*, **36:** 1213, 1954.

103. Musajo, L., Rodighiero, G., Caporale, G. and Antonello, C.: Relation between constitution and photodynamic properties of furocoumarins. *Farmaco (Pavia), Ed. Sci.*, **13:** 355, 1958. (Italian)

104. Pathak, M. A.: Mechanism of psoralen photosensitization and *in vivo* biological action spectrum of 8-methoxypsoralen. *J. Invest. Derm.*, **37:** 397, 1961.

105. Buck, H. W., Magnus, I. A. and Porter, A. D.: The action spectrum of 8-methoxypsoralen for erythema in human skin. *Brit. J. Derm.*, **72:** 249, 1960.