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 (bergaptten)) 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. Fowiks 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, Fowiks (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 psoralsens (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 trypanflavin. 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 parsley, 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 processors (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., “herlogue dermatitis” which is the reaction to 5-methoxy-psoralen 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 Agrimonia 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.

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<th>No.</th>
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<th>References</th>
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<tbody>
<tr>
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<td>2.</td>
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<td>Petroselium sativum</td>
<td>Garden parsley</td>
<td>Umbelliferae</td>
<td>8, 39, 57</td>
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</table>
3. 8-Methoxypsoralen (Xanthotoxin or Methoxalen or Ammoidin)

![Chemical structure of 8-Methoxypsoralen]

- Ammi majus (Bishop's weed) - Umbelliferae
- Angelica archangelica (Engelwurz) - Umbelliferae
- Pastinaca sativa (Garden parsnip) - Umbelliferae
- Ficus carica (Fig) - Moraceae
- Ruta chalepensis - Rutaceae
- Fagara xanthoxyloides - Rutaceae
- Ruta montana - Rutaceae
- Aegle marmelos - Rutaceae
- Ruta graveolens - Rutaceae
- Luvanga scandens - Rutaceae
- Xanthoxyllum flavum

4. 8-Isopentenyloxypsoralen (Imperatorin or Ammidin)

![Chemical structure of 8-Isopentenyloxypsoralen]

- Ruta bracteosa - Rutaceae
- Imperatoria ostruthium - Umbelliferae
- Angelica glabra - Umbelliferae
- Angelica archangelica - Umbelliferae
- Ammi majus - Umbelliferae
- Peucedanum ostruthium - Umbelliferae
- Pastinaca sativa - Umbelliferae
- Prangos pabularia - Umbelliferae
- Aegle marmelos - Umbelliferae
- Ruta chalepensis - Umbelliferae

5. 5,8-Dimethoxypsoralen (Isopimpinellin)

![Chemical structure of 5,8-Dimethoxypsoralen]

- Pimpinella saxifraga (Cow parsley) - Umbelliferae
- Heracleum sphondylium (Cow parsley) - Umbelliferae
- Sesli indicum - Umbelliferae
- Skimmia laureola - Rutaceae
- Citrus aurantifolia (West Indian lime) - Rutaceae
- Luvanga scandens - Rutaceae
- Thamnosma montana - Rutaceae
- Fagara ollanthoides - Rutaceae
- Heracleum lanatum (var. nipponicum)
- Citrus acida (Lime) - Rutaceae

DISTRIBUTION OF PUROCOMARINS IN PLANTS


<table>
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<tr>
<th>No.</th>
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<td>6.</td>
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<td>4'-Methoxy-5'-isopropylpsoralen (Peucedanin)</td>
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<td></td>
<td>Prangos pabullaria</td>
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<td>Prangos pabularia</td>
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10. Oreoselone

\[
\begin{align*}
& \text{Peucedanum officinale} \\
& \text{Peucedanum oreoselinum} \\
& \text{Masterwort} \\
& \text{Umbelliferae} \\
& 29 \\
& 78
\end{align*}
\]

11. Ostruthol

\[
\begin{align*}
& \text{Peucedanum ostruthium} \\
& \text{Masterwort} \\
& \text{Umbelliferae} \\
& 28, 29, 37, 79
\end{align*}
\]

12. 5-Methoxy, 8-isopentenyloxypsoralen (Phellatorin)

\[
\begin{align*}
& \text{Angelica glabra} \\
& \text{Phellopterus littoralis} \\
& \text{Umbelliferae} \\
& 29
\end{align*}
\]

13. 4',5-dihydro, 5'-(1-glucosoxy-isopropyl) psoralen (Nodakenin)

\[
\begin{align*}
& \text{Peucedanum decursivum} \\
& \text{Umbelliferae} \\
& 37, 80
\end{align*}
\]
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<td>18.</td>
<td>5-Methoxy-8-epoxyisopentenyloxypsoralen</td>
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<td>(Byak angelicol)</td>
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27. \(4',5'-\text{Dihydro-5'}-(1\text{-hydroxyisopropyl}),4'-\text{hydroxy-diisovaleryl ester}\) Athamanta oreoselinum
Peucedanum oreoselinum
(Umbelliferae)

H\(_2\)C
C—OCOCH\(_2\)CH(CH\(_3\))\(_2\)

H\(_2\)C
C—OCOCH\(_2\)CH(CH\(_3\))\(_2\)

O
CH\(_2\)

O

Athamanta oreoselinum
Peucedanum oreoselinum
(Umbelliferae) 87
(Umbelliferae) 29, 87
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 phytophotogenic 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 mantegazzianum.*

<table>
<thead>
<tr>
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<th>Botanical Name</th>
<th>Natural Order</th>
<th>References</th>
</tr>
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<tr>
<td>Garden parsnip</td>
<td>Heracleum gigantum</td>
<td>Umbelliferae</td>
<td>13, 91, 92</td>
</tr>
<tr>
<td>Wild parsnip</td>
<td>Pastinaca sativa</td>
<td>Umbelliferae</td>
<td></td>
</tr>
<tr>
<td>Wild carrot</td>
<td>Daucus carota</td>
<td>Umbelliferae</td>
<td>10, 11, 13</td>
</tr>
<tr>
<td>Garden carrot</td>
<td>Daucus sativa</td>
<td>Umbelliferae</td>
<td>15, 93</td>
</tr>
<tr>
<td>Masterwort</td>
<td>Peucedanum ostruthium</td>
<td>Umbelliferae</td>
<td>25</td>
</tr>
<tr>
<td>Celery</td>
<td>Apium graveolens</td>
<td>Umbelliferae</td>
<td>10, 88, 94</td>
</tr>
<tr>
<td>Atrillal</td>
<td>Ammi majus</td>
<td>Umbelliferae</td>
<td>95</td>
</tr>
<tr>
<td>Angelica</td>
<td>Angelica species</td>
<td>Umbelliferae</td>
<td>13</td>
</tr>
<tr>
<td>Common rue</td>
<td>Ruta graveolens</td>
<td>Rutaceae</td>
<td>10, 96</td>
</tr>
<tr>
<td>Gas plant</td>
<td>Dictamnus albus</td>
<td>Rutaceae</td>
<td>97</td>
</tr>
<tr>
<td>Lime bergamot</td>
<td>Citrus bergamia</td>
<td>Rutaceae</td>
<td>10, 11, 13</td>
</tr>
<tr>
<td>Lime</td>
<td>Citrus aurantiom</td>
<td>Rutaceae</td>
<td>10</td>
</tr>
<tr>
<td>Lime</td>
<td>Citrus aurantifolia</td>
<td>Rutaceae</td>
<td>10, 14</td>
</tr>
<tr>
<td>Persian lime</td>
<td>Citrus aurantifolia, var. Swingle</td>
<td>Rutaceae</td>
<td>10, 14</td>
</tr>
<tr>
<td>Buttercup</td>
<td>Renunculus species</td>
<td>Renunculaceae</td>
<td>10, 13</td>
</tr>
<tr>
<td>Mustard</td>
<td>Brassica species</td>
<td>Cruciferae</td>
<td>11, 13</td>
</tr>
<tr>
<td>Blind weed</td>
<td>Convolvulus arevensis</td>
<td>Convolvulaceae</td>
<td>10, 11, 92</td>
</tr>
<tr>
<td>Agrimony</td>
<td>Agrimony eupatoria</td>
<td>Rosaceae</td>
<td>10</td>
</tr>
<tr>
<td>Yarrow (milfoil)</td>
<td>Achilleae millefolium</td>
<td>Compositae</td>
<td>10</td>
</tr>
<tr>
<td>Goose foot</td>
<td>Chenopodium species</td>
<td>Chenopodiaceae</td>
<td>11, 13, 99</td>
</tr>
<tr>
<td>Bavaehi</td>
<td>Psoralea coryfolia</td>
<td>Leguminose</td>
<td>28, 95</td>
</tr>
<tr>
<td>St. John's wort</td>
<td>Hypericum perforatum</td>
<td>Hypericaceae</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Hypericum concinnum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 oxypeucedanin. 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 Hinrencher (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, angelica, isobergapten and pimpinellin do not induce erythema. Psoralen, xanthotoxin, bergapten, isoirmpatorin 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, phellaportin, nodakenin, oreoselone, thamnosmin, byak angelicol, byak angelin, 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, coriander, 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 Compositae, Cruciferaceae, 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 erythematic photosensitization response are in the range between 340 and 380 μμ, with maximum effectiveness at 360 μμ. Various plant species reported to cause photosensitization (Table 2) have been analyzed by several workers and shown to contain furocoumarins, especially xanthotoxin, bergaptin, psoralen, etc. These compounds are highly photosensitizing and cause dermatitis and residual pig-
mentation. 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 contain 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.

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