Some of man's earliest research efforts were concerned with attempts to restore the normal skin color to scattered, pigment-less areas considered to be leprosy, although most of which were probably vitiligo. In the Indian sacred book *Atharva Veda*, which dates back to 1400 B.C. or earlier, the "cure" of leprosy and leukoderma (vitiligo) with certain black seeds together with Bringarāga (*Eclipta prostrata*), Indravaruni, (*Colocynthis*), and turmeric (*Curcuma longa*) has been described in detail. The importance of the problem is illustrated by the following ode to one of the plants used, described in the *Atharva Veda* (1, 2).

Born by night art thou, 0 plant,
Dark, black, sable, do thou,
That art rich in color, stain
This leprosy and white gray spots.
Even color is the name of thy mother,
Even color is the name of thy father.
Thou O plant producest even color
Render this (spot) to even color.

The plant alluded to is not precisely known, but when one reads other ancient Indian medical literature such as *Aṣṭanga-Hṛdaya Samhitā* by Vagbhata, or *Medicine*, a large German encyclopedia of Indo-Iranian studies (3), it would appear that the most widely used plant was Bava-chee, a species containing psoralen.

In the Bower manuscript translated by A. F. R. Hoernle (4) which deals with manuscript remains of Buddhist literature found in Eastern Turkestan and the studies of medicine in ancient India (about 200 A.D.), the cure of leukoderma with the plant known as "Vasuchika" (said to be an old form of *Bavachee* or *Psoralea corylifolia*) has been distinctly mentioned. In "Sino-Iranica"

Another important plant, *Ammi majus*, a weed found in the Nile Valley, has been employed for centuries as a "cure" for leukoderma. Ibn El Bitar, who lived in the thirteenth century, gave a description of the usefulness of this plant for leukoderma in his famous book, "Mofradat El-Adwiya" (6). This plant was used by "Ben-Shoeib" a Berberian tribe in the Northwestern African desert.

The modern period of psoralen research began in 1938 when Kuske investigated "phytophotodermatitis", a bullous eruption appearing on the areas of the skin which have been in contact with certain plants and subsequently exposed to sunlight (7). He obtained pure compounds by extraction of oil of bergamot (bergapten), masterwort or *Peucedanum ostruthium* (oxyruecedenin), and figs (ficusin or psoralen).

Extensive research on psoralens began in 1941 in the laboratories of Fahmy and his group at the University of Cairo, Egypt. Fahmy observed that some Egyptian herb doctors were using a gray-green powder called "Atrillal" for the treatment of vitiligo. It was distributed through only one or two dealers who would not reveal its nature. Fahmy later ascertained that "Atrillal" powder was obtained from the fruits of a weed growing along the Nile delta called *Ammi majus* L. Fahmy and Abu-Shady in 1947
isolated three crystalline compounds which they believed were the active ingredients of the crude powder (8). These were found to be furocoumarins and were named from the plant from which they were obtained (Ammi majus L.): ammoidin, ammidin and majudin. This was an unfortunate selection of names for two of the compounds had already been known. Ammoidin, or 8-methoxypsoralen, had been isolated in 1911 from a different plant source (9) and synthesized in 1933 by Späth (10). Majudin, or 5-methoxy-psoralen, was a well-known constituent of oil of bergamot which had long been used in the perfume industry.

Fahmy then engaged an excellent young Egyptian dermatologist, El Mofty, to carry out a clinical trial of the three compounds in the treatment of vitiligo. The results were encouraging (11), and shortly afterward two of the compounds, 8-methoxypsoralen and 8-isoamyleneoxypsoralen, were marketed by an Egyptian firm in Cairo. This firm distributed tablets and a topical liquid containing the two drugs. Confirmation of El Mofty’s results were reported in France (12, 13). However, some difficulty was encountered in introducing the drugs into the United States, and only one pharmaceutical firm started clinical trials of 8-methoxypsoralen (generic name, methoxsalen) in this country. In 1951, Pinkus began a study of topical methoxsalen in the treatment of vitiligo (14). Lerner, Denton and Fitzpatrick (1952) at the University of Michigan used the drug orally in nine vitiligo patients with moderate success (15). In the course of this study, a curious effect was noted in two of the vitiligo patients. These patients, who were brothers engaged in farming, noted that they were able to tolerate sunlight on the vitiligo areas much better than before the treatment. In addition, three albinos, who were then given methoxsalen, commented on an increased tolerance to sunlight. Fitzpatrick and Lerner (1954) had the opportunity to treat a physician’s wife with vitiligo at the University of Oregon Medical School in November, 1952. The patient declared that ingestion of methoxsalen before exposure to sunlight substantially enhanced the tanning response of her normal-appearing skin.

From 1952–54, Fitzpatrick and Lerner used methoxsalen orally in the treatment of 110 vitiligo patients and extended the testimonial-type evidence of increased sun tolerance of vitiligo skin following treatment (16). In addition, 36 normal persons claimed increased tanning and decreased sunburn while using 20 mg. of methoxsalen daily. Because of the testimonial type of evidence, it was decided to carry out controlled studies of the apparent augmented tanning and increased solar tolerance following oral methoxsalen. The results of earlier controlled experiments have been reported (17). Meanwhile, Musajo (1955) in Italy had reported the relative activity of many furocoumarins and coumarin derivatives applied topically to human skin (18).

It became apparent that methoxsalen or one of the furocoumarins might possibly be developed as an oral drug to increase the tolerance of human skin to sunlight. Because of the important basic and clinical implications of this hypothesis, a fairly extensive research effort was begun in a few medical centers on the botanical sources of furocoumarins, their mechanism of action, their toxicity in animals and man, the development of high intensity, monochromatic ultraviolet sources, and the effect of furocoumarins on the incidence of solar or ultraviolet-induced skin cancer in man and mice. As a result, considerable information is now available on some of the phases mentioned above, although many aspects remain to be clarified.

The notion that an orally ingested compound could alter the tolerance of man to solar radiation appears to be following the pattern of hypotheses which, according to William James, pass through three classic stages:

First, a new hypothesis is attacked as absurd;
Second, it is admitted to be true but obvious and insignificant;
Finally, it is seen to be so important that its adversaries claim that they themselves discovered it.

The furocoumarin hypothesis is at present in the first of these stages with symptoms of the second stage having begun in a few quarters.

REFERENCES


Clinical Pharmacokinetics of Methoxsalen and Other Psoralens. The psoralen derivative methoxsalen and to a lesser extent some other furocoumarin congeners, including bergapten and trioxsalen, have acquired a place in the treatment of psoriasis and other dermatoses. They are inactive after oral or more. The psoralen derivative methoxsalen and to a lesser extent some other furocoumarin congeners, including bergapten and trioxsalen, have acquired a place in the treatment of psoriasis and other dermatoses. They are inactive after oral or topical administration unless combined with irradiation w Part IV: Basic Considerations of the Psoralens: Historical Aspects of Methoxsalen and Other Furocoumarins 1. Article. Feb 1959. Oral administration of a photoactive drug, 8-methoxypsoralen (methoxsalen), followed by exposure to a high-intensity, longwave ultraviolet-light system resulted in complete clearing of generalized psoriasis in 21 patients. In 16 of these cases, a paired comparison showed methoxsalen followed by longwave ultraviolet light to be more effective than conventional ultraviolet light. 8-Methoxypsoralen followed by exposure to longwave ultraviolet light has previously been shown to inhibit epidermal DNA synthesis; this may be its mechanism of action in psoriasis, a disorder characterized by an acceler