

Rue the Herb: *Ruta graveolens*–Associated Phytophototoxicity

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We describe an unusual case of phytophototoxicity induced by an herbal plant, *Ruta graveolens*, from the Rutaceae family. This common herb, also called rue, can be found throughout rural settings in the United States. When psoralens from rue come in contact with human skin that is subsequently exposed to ultraviolet A light, an impressive photoirritant reaction can occur. This report both clarifies the distinguishing features of photoirritant reactions versus photoallergic reactions and reviews the pathophysiology and clinical presentation of phytophotodermatitis. *R. graveolens* can be associated with an impressive photoirritant reaction and should not be used as an insect repellent.

“THIS HERBAL PLANT has been used for centuries as a mosquito repellent; it is said that its pungent odor wards off insects. Pick the flowering plant from the grass beside you and crush all of its parts in your hands. Then rub the plant’s oils all over your skin,” instructed the leader of an August Native American storytelling and crafts workshop in upstate New York. “This will keep the mosquitoes away!” All four adults and seven children (aged 4 to 9 years) picked the herb (Fig 1) from the grass upon which they sat and did as their leader had instructed. Little did they know what would follow.

All of the workshop participants, without the instructor, spent the remainder of the afternoon in the midday sun. The majority of the group returned to a family pool, where a sunscreen with a sun protective factor (SPF) of 30 was applied to all the children throughout the day as they played without signs or symptoms. However, only 24 hours after their Native American “experience,” some of the group’s participants, especially the younger children, began to develop purple-red patches on various areas of their bodies. Most of their skin changes were in a linear pattern, representing where they had dragged and rubbed the *Ruta graveolens* plant and its oils in an up-and-down motion (Fig 2).

These patches soon transformed into tense bullae, some the size of “large potato chips.” One child developed a violaceous patch that encompassed the entire underside of

her arm. In this instance, the plant oils had been thoroughly rubbed into the skin in a circular manner. One of the older children showed no dermatologic findings until 4 days later, when numerous linear patches (portions of which later blistered) appeared; this child was described by her mother as looking “as if she had been attacked by a bear.” For some individuals, new areas of blistering continued to erupt for as long as 10 to 12 days after the initial exposure.

Adults and those children who had spent more of the day in the shade seemed less affected and had very few blisters. Still, many of the parents did experience macular or patchy lesions 4 to 6 cm in diameter (and described by family members as “bruise-like”) on their extremities. The bullae lasted for as little as a few days to as long as a few weeks. Some recalled a “burning tingling sensation” just prior to the manifestation of the rash, but only after changes in the skin were visible did localized physical pain become a symptom. The pain was described as “what you would expect with a physical or chemical burn.” One adult also experienced pruritus both as the rash appeared and as it healed.

The majority of affected individuals were seen by their primary care physicians. Three required a systemic pulse of oral prednisone while others were treated with oral cetirizine and diphenhydramine, topical hydrocortisone 2.5% cream twice daily, and oatmeal baths. Those who received oral steroids experienced no further development of vesicles or bullae. However, even 2.5 months after the initial rue-related skin eruption, areas of both hyper- and hypopigmentation still remained at the sites of previously blistered skin (Fig 3). Interestingly, patients also reported that the lesional skin, now mostly patches of light brown

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Figure 1. *Ruta graveolens*.

postinflammatory pigmentation, still reacted with increased erythema and sensitivity when exposed to sunlight, fluorescent light, heat, or exercise.

Discussion

Contact dermatitis has long been associated with a wide array of different types of plant life. Sun exposure also commonly plays a similar role in adverse skin reactions. More rare, however, is the occasion when simultaneous exposure to both plant chemicals and ultraviolet light is needed to cause skin injury. Contact dermatitis resulting from exposure to plants containing chemicals called psoralens or furocoumarins, followed by ultraviolet light exposure to those same areas, is called phytophototoxicity.¹ Histologically, this photoirritant contact dermatitis may manifest as epidermal intracellular or intercellular edema with necrotic keratinocytes. Depending on the severity of the toxicity, subepidermal bullae may also be present.²

Phytophototoxicity is an irritant/toxic type of photocontact dermatitis. The reaction requires no prior sensitization to the provoking agents and occurs in all exposed individuals when exposure to both light and the plant chemical has been sufficient. Irritant photocontact dermatitis is not to be confused with allergic photocontact dermatitis, which occurs only in individuals who are genetically susceptible to the allergen; allergic photocon-



Figure 2. Linear hyperpigmented patches on a patient's right leg, 10 weeks after exposure.



Figure 3. Linear hypopigmented patches along the left arm of a child.

tact dermatitis does not occur in all exposed individuals. Additionally, an allergic-type reaction requires the synthesis of a photoallergen (an antigenic molecule) to begin the cascade of a delayed cellular hypersensitivity. Thus, only on reexposure to the allergen does a skin reaction occur.² Furthermore, phototoxic disorders have a high incidence whereas photoallergic reactions are much less frequent.³ We describe here an unusual case of phytophototoxicity induced by *Ruta graveolens*, an herbal plant from the Rutaceae family.

R. graveolens, an herb commonly known as rue, has for centuries been responsible for causing skin irritation.⁴ Although indigenous to southern Europe, this evergreen shrub can be found worldwide.⁵ Its blue-green leaves emit a pungent odor and are bitter to the taste.⁶ Ironically, the herb and its flower, stem, and leaf components have long been used for their various medicinal and miraculous properties. This long list of uses includes the plant's use as an antiinflammatory and analgesic in treating systemic infections, eczema, external ulcers, rheumatism, and cramps; as an antidote for snake and scorpion venom; as an herbal decoction for fending off evil spirits; and as an insect repellent.^{5,7–11} *R. graveolens* has even been used as an herbal seasoning in cooking and as the main component in soaps, creams, and perfumes.⁵

R. graveolens contains numerous chemicals, including essential oils, furocoumarins (eg, bergapten, psoralen, and imperatorin), carotenoids, chlorophyll, and antimicrobial alkaloids called furoquinolines.^{5,12–14} Bioassays performed by Hale and colleagues on the leaves of *R. graveolens* determined three primary phototoxic agents: the furanocoumarins 5-methoxypsoralen (5-MOP) and 8-methoxypsoralen (8-MOP) and the quinolone alkaloid graveoline. Of these, 8-MOP had the greatest phototoxicity.⁶ A linear furocoumarin, 8-MOP (xanthotoxin) is a well-known photoirritant.^{2,15} This compound and 5-MOP are also presently used in combination with ultraviolet A (UVA) radiation (320–400 nm) as photochemotherapy for the treatment of cutaneous T-cell lymphoma, psoriasis, and vitiligo.^{1,6,12,15,16}

Paradoxically, it is accidental exposure to these same medically used plant psoralens that sensitize and harm the skin in other phytophototoxic reactions. The psoralen chemicals are transferred from plant to human skin in any activity that involves bruising, cutting, damaging, or touching the foliage.¹ Then, in the presence of ultraviolet light, the plant's psoralen chemicals bind to human pyrimidine bases of deoxyribonucleic acid (DNA), causing phototoxic injury to the skin via the inhibition of mitosis.^{6,17} Subsequent cell death can manifest as severe

skin damage.^{6,17–19} Studies designed by Ojala and colleagues to quantify the phototoxicity of different plant parts showed that *R. graveolens* is three times as phototoxic after flowering, when coumarin content is at its peak.¹⁷

A typical phytophototoxic reaction includes erythema, edema, and burnlike lesions within 24 hours and potentially large fluid-filled blisters within 48 to 72 hours.^{1,2} Psoralens tend to produce a more delayed photoirritant effect.² Depending on (1) the extent of exposure to sun and (2) the quality and quantity of contact with plant leaves, sap, stems, or flowers, phototoxic reactions range from minor linear hyperpigmentation of the skin to large painful bullae. Symptomatic complaints often include pruritus or burning skin, as was experienced by many of our case patients.

After intense or concentrated exposure that results in a fulminant blistering response, resolution of the pain and bullae usually occurs within a few days to about 1 week. However, in severe cases in which systemic stability is threatened, hospitalization may be required.⁵ With time, the initial irritation, erythema, and edema slowly decrease, leaving areas of dyspigmentation. It is not uncommon for residual dyschromia to last for months, and permanent scarring is a possible outcome.^{20–22} Several of our patients actually reported areas of both hyper- and hypopigmentation in previously blistered skin. Most notable, though, is the continual increased sensitivity of lesional skin with further reexposure to ultraviolet light, potentially for years.^{20–22}

In diagnosing phytophototoxic reactions, history and clinical presentation are critical. These tools alone should lead the dermatologist to the correct diagnosis, and photopatch testing should be avoided entirely. The caveat here is that psoralens are photoirritants and will affect *all* exposed individuals.² Unfortunately, management of photocontact dermatitis is fairly limited to supportive and symptomatic care.

If phytophototoxicity is suspected before the appearance of the skin changes, soap and water should be used to wash off the plant chemical from the area of contact; thereafter, application of sunscreen and abstention from sun exposure are strongly encouraged for the following 48 hours.¹ Once photocontact dermatitis is apparent, therapy can include antihistamines, soothing baths to mitigate pruritus, and topical corticosteroid creams. Depending on the reaction's severity, oral or intravenous steroids are a consideration.⁵ In addition to regular preventative skin care in regard to exposure to the sun, patients with a history of phytophotoreaction should also use sunscreen prophylactically to prevent reexposure sensitivity.

Additionally, because the spectrum for psoralen activity is within the UVA range, patients should be cautioned that glass windows are not protective against future UVA reexposure and the accompanying dermatitis flare.²

Summary

We present an unusual case of *Ruta graveolens* phytophotodermatitis through the course of exposure, evolution of dermatitis, treatment, and follow-up, all in an extended family. This case is not entirely unique. Similar cases of irritant photocontact dermatitis induced by using *R. graveolens* leaves to ward off unwanted mosquitoes in Oregon and Scotland have been reported.^{10,11} Others have also espoused the efficacy of *R. graveolens* as an insect repellent.²³ Despite the numerous literary citations of the “limitless uses” of *R. graveolens*, one may want to seriously reconsider “following the leader” before coming into contact with this potentially phototoxic herb.

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