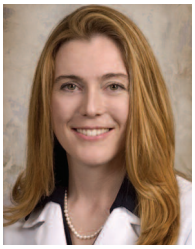
ALLERGEN Focus

NACDG Allergens: *Compositae* Mix and Sesquiterpene Lactones

BY SHARON E. JACOB, M.D., AND TAMAR ZAPOLANSKI, B.A.

In 1997 the Food and Drug Administration gave indication to the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) test for use as a valuable, first-line screening tool in the diagnosis of allergic contact dermatitis (ACD). Many dermatologists and allergists use this standard tool in their practices and refer to contact dermatitis referral centers when the T.R.U.E test fails to identify a relevant allergen. Specifically, the T.R.U.E. test screens for 46 distinct allergens in addition to the balsam of Peru mixture, and it is thought to *adequately identify an allergen in approximately 24.5%* of patients.[1] This being said, many relevant allergens are not detected by use of this screening tool alone and, for this reason, "Allergen Focus" has been expanded to cover the notorious Allergens of the Year and other top relevant allergens identified by the North American Contact Dermatitis Group.



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This month, we focus on compositae mix, sesquiterpene lactones and parthenolide, which are extracts from plants in the *Asteraceae* family (also known as the *Compositae*). These plants include asters, daisies and sunflowers, and they're used as herbal medicine remedies for their anti-inflammatory activities. Many of these extracts are used in topical skin treatments and cosmetics. In addition, substances from these plants are frequently ingested as food and drink, herbal supplements, and alternative therapies. Here, we will discuss some background on herbal remedies and specific information about those used in the *Asteraceae (Compositae)* family.

CASE ILLUSTRATION

A patient presented to the University of Miami Contact Dermatitis Clinic for evaluation of a dermatitis primarily involving his fingertips. He had been evaluated with the T.R.U.E. test and no positive allergic reactions were found. Of note, his hobby was preparing weekly sunflower arrangements, which were displayed in his foyer.

HISTORY OF HERBAL MEDICINE

Throughout history, laypeople, herbalists, and healers have turned to plants in search of cures for medical ailments. Herbalism, the folk medicinal practice based on the utilization of botanical therapeutics, is generally perceived as a universal practice among a wide range of cultures.

In Homer's *The Odyssey,* evidence of the ancient Greeks and Egyptians sharing knowledge of herbal treatments is purveyed: "Such cunning drugs had the daughter of Zeus, drugs of healing, which Polydamna… had given her, a woman of Egypt, for there the earth… bears greatest store of drugs, many that are healing…"

Furthermore, the *Characha Samhita*, an ancient Indian medical text, describes

hundreds of herbs used for healing purposes. Similar writings have been uncovered in China, such as *Prescriptions for Fifty-Two Ailments*, a work that names more than 250 medicinal substances.

Pedanius Dioscorides, a noted first-century Greek physician, is known to have traveled the ancient world in search of therapeutic herbals. He was among the first to describe the use of *Tanacetum parthenium*, also known as feverfew (a member of the *Asteraceae* family native to southeastern Europe), as a treatment for "all hot inflammations and hot swellings" from arthritic pain, headaches and menstrual irregularities to stomachache and fevers. Interestingly, the use of this herb as an antipyretic is what led to its being commonly referred to as *feverfew*, a corruption of the Latin *febrifugia*, or fever reducer (circa 1400 A.D.).

Dioscorides went on to write *De Materia Medica*, a noteworthy five-volume set of texts. This is said to be one of the most comprehensive herbal volumes in history, because it described the curative properties and possible side effects of more than 600 plants, which were accompanied by drawings. Additionally, these texts are considered some of the most influential in the area of herbal remedies, and they remained in continuous circulation for longer than 1,500 years![4]

More than 15 centuries later (c. 1597), an English apothecary and surgeon, John Gerard, published his famous text, *Herball*, which was partially based on Dioscorides' *De Materia Medica*. As a physician and avid gardener, Gerard wrote about plants and their medicinal properties. In addition, Gerard noted their decorative qualities and laced his book with beautiful botanical illustrations. He also included plants of culinary and economic significance, such as the potato.

Unfortunately, Gerard was in such a hurry to publish his works that he made many errors. But, in 1633, Thomas Johnson published a second edition of Gerard's *Herball* in which he corrected many of the errors, improving both the accuracy and utility of the book. Johnson also added more than 800 new plants and 700 additional illustrations.

As Dioscorides had done before him, he described using feverfew to treat migraine headaches: "it is very good for them that are *Giddie* in the head, or which have the turning called *Vertigo*, this is a swimming and turning in the head."[5]

Ultimately, the popularity of this herb waned, and herbalism fell out of favor in the late 18th and 19th centuries as allopathic medications were becoming more readily available and more mainstream.

THE USE OF THIS HERB AS AN ANTIPYRETIC IS WHAT LED TO ITS BEING COMMONLY REFERRED TO AS *FEVERFEW*, A CORRUPTION OF THE LATIN *FEBRIFUGIA*, OR FEVER REDUCER.

And although the public began to turn to herbals again in the early 20th century, it was not until the wife of a Welsh doctor ended her 50-year history of migraines with feverfew that the scientific community again became interested in this plant.

Mrs. A. Jenkins had been suffering from migraines her entire life when a coal miner told her that feverfew cured migraines. Mrs. Jenkins began drinking feverfew tea, three leaves per day, and after about 10 months her migraines subsided. Her story, published in *Prevention* magazine in 1978, sparked renewed interest in this plant, and in the 1980s the British began investigating the effectiveness of feverfew for migraine therapy.

In recent years, a resurgence in alternative and complementary medicine practices has occurred in both modern Eastern and Western cultures and renewed interest in finding cures and therapies from botanical sources.

COMPOSITAE HERBALS AS MEDICINALS

In 1985 a group of researchers from the City of London Migraine Clinic and Chelsea College at the University of London performed the first controlled experiment on feverfew as prophylactic treatment of migraines. Using volunteers who were already taking feverfew for their migraines, the researchers organized a double-blind study. Some patients continued to receive feverfew, while others were given placebo.

Those taking placebo suffered an increase in the frequency and severity of headaches, nausea, and vomiting within the first few months of treatment.[6] This suggested that feverfew taken prophylactically can indeed prevent migraine attacks. Subsequent randomized double-blind placebo-controlled trials have confirmed the efficacy of feverfew for migraine therapy.

Since then, interest has risen in isolating the active ingredients and the mechanisms of actions for the extracts of feverfew.

One extract, **parthenolide**, has been found to inhibit platelet aggregation and the release of serotonin from platelets. Migraines are associated with abnormal platelet function, namely increased aggregation and release of serotonin, which can result in vasodilatation. Therefore, it is thought that through this pathway parthenolide can normalize blood vessel tone, decreasing the frequency of the migraines and alleviating the symptoms associated with these headaches.[7]

Many other botanicals are also known to have medicinal qualities. *Arnica (arnica Montana)* is widely used throughout Europe as an anti-inflammatory and to promote wound healing. Great burdock (*arctium lappa*) also is known to have anti-inflammatory properties and in some cases is used as a topical wash for psoriasis and acne. Commonly known for its use as a tea infusion, chamomile (*Chamomilla recutita, Chamomilla nobile, Anthemis cotula*) is also purported to have spasmolytic, anti-inflammatory, and anxiolytic effects. In addition to being ingested as a tea, medicinal preparations of chamomile also include the essential oil of the plant and wet compresses of chamomile. Notably, all of these botanicals belong to the same family: *Asteraceae*.

THE *ASTERACEAE* FAMILY

Asteraceae, commonly known as the daisy or sunflower family, derives its name from the Greek root "aster" meaning "star", because many of the flower heads of these plants are star-shaped.

While this descriptive term is the official name designated by the International Code of Botanical Nomenclature, it is one of the nine botanical families with an accepted alternative name (an exception made for families with a long history of reference by another name).

In the case of the *Asteraceae*, they are also referred to as the *Compositae* family, a name referring to their unique structural "heads" characterized by a composite network of grouped individual flowers. More than 20,000 different species of flowers, herbs, vegetables and weeds belong to this taxon of flowering plants. (**See Table 1**) Notably, it is second only to the orchid family (*Orchidaceae*) in terms of being the largest plant family, representing 10% of the world's flowering plants.[8]

DIVERSITY OF *COMPOSITAE*

The diversity of this plant family ensures that daily contact with *Asteraceae* is nearly inevitable. Some are topically applied to the skin as treatments and cosmetics. Many of these plants are ingested as food and drink, herbal supplements, and alternative therapies. Many are consumed in the form of teas (i.e. chamomile, sunflower, chrysanthemum).

Rodriguez-Serna et al reported a case of allergic-systemic contact dermatitis due to chamomile tea. A patient with a history of topical chamomile use was tested with a plant patch series. She had positive reactions to SL mix, *Achillea millefl ium*, and *Tanacetum vulgare*. Two weeks later, the patient presented with a flare-up of her cutaneous lesions, edema and itching of the oral mucosa, eczema, and anal pruritus. It was noted that the patient had ingested a cup of chamomile tea the day before presentation.[9]

This case demonstrated that chamomile can lead to dermatitis following systemic exposure and minimal amounts of antigen, such as that found in tea.

Exposure can vary due to seasonal changes in blooming and pollen levels resulting in a seasonal contact dermatitis. Frequently, such a patient's dermatitis worsens in the summer months, when many *Asteraceae* flowers are in bloom. Ingber presented a case of a florist with pruritic erythematous lesions on her hands for 2 years, which notably appeared in the summer and cleared in the winter. This patient was patch-test positive to *Taraxacum officinale* (dandelion), which bloomed at warmer temperatures and therefore explained her seasonal dermatitis pattern.[10]

Additionally, individuals are frequently unaware of their contact with *Asteraceae* because some species produce copious amounts of airborne pollens, resulting in inhalation exposure as well. Mahajan et al presented a case of a male office worker with a history of erythemato-squamous pruritic rash with associated painless lymphadenopathy. The patient's condition improved while staying in a parthenium-free region.

Since the clinical picture did not agree with the classic pattern of airborne contact dermatitis, the patient was asked to inhale from a bag containing parthenium to confirm the hypothesis that his allergy was due to inhalation and not direct contact. Within 8 to 10 hours after inhalation, the patient developed widespread pruritus and dermatitis over the lower extremities.[11]

REACTIONS TO *COMPOSITAE* HERBALS

While many herbs, including parthenium, may be quite effective as therapeutics, it is essential to consider their possible adverse effects, just as with conventional medications. Many cases of contact dermatitis to parthenium have been published. The leaves of the plant can be taken orally and may cause inflammation of the mouth, tongue, and lips. Additionally, patients frequently develop oral ulcers.[12]

In addition to classic contact and systemic dermatitis, parthenium can result in airborne contact and inhalation dermatitis. Many individuals may experience occupational sensitization with exposure to airborne pollen or decorative plants. In severe cases patients may develop prurigo-nodularis-like lesions.

In one case, a male deputy collector had a 4-year history of pruritic erythematous papules on his face, neck and forearms and presented with papulonodules over his forearms and legs. Patch tests were positive to parthenium.[13]

ALLERGENS OF THE *COMPOSITAE* FAMILY

Sesquiterpenes are essential oils common to all members of the *Asteraceae* family. These oils exert the major allergenic effects of this plant family. The subtype of sesquiterpenes that most commonly causes dermatitis is the lactones, or sesquiterpene lactones (SLs). These lactones have a sesquiterpene skeleton, a hydrocarbon, and a lactone ring.

Notably, the aforementioned allergenic component of parthenium, parthenolide, is an SL. Also as mentioned above, some of these plants are consumed in the form of teas, and evidence of SLs in the tea preparations has been demonstrated.[14]

For example, although essential oil of chamomile is poorly water soluble, and tea only contains 30% to 45% of the oil, SLs are present in the brew.[15]

TESTING FOR *ASTERACEAE* ALLERGY

Sesquiterpene lactone mix (SL mix), a 0.1% mixture of equal parts of three different lactones in a petroleum base, can be applied as a patch test to screen for *Asteraceae* allergy. In 1990 a large-scale patch test study with SL mix was performed, and it was established as an important screening agent for *Asteraceae* allergy.

However, many case reports demonstrated that SL mix does not detect all cases of sensitization. Subsequent studies have also established that patch-testing alone with SL mix may not be sufficient to diagnose all cases of *Asteraceae* dermatitis.[16] In order to increase the sensitivity of the patch test screening substance, SL mix has been supplemented with both ***Compositae* mix** (CM) and with other *Compositae* extracts.

Paulsen et al reported on their 8-year experience in Denmark using both SL mix and CM, a 6% petroleum mix of chamomile, tansy, yarrow, arnica, and feverfew extracts. Patients were tested with either or both mixes where appropriate. In the report, SL mix detected 65% and *Compositae* mix 87% of *Compositae*-allergic patients. Together the detection rate was 93%, and they concluded that the SL mix detection rate warranted its continued use as a screening mix, and that supplementation with

TABLE 1

SELECTED MEMBERS OF THE *ASTERACEAE* PLANT FAMILY (COMMON NAMES)

- Chamomile
- Feverfew
- Arnica
- Marigold
- Dandelion
- Sunflower
- Chrysanthemum
- Lettuce
- Artichoke
- Daisy
- Chicory
- Ragweed
- Burdock

CM should be done to increase the detection rate in high-risk patients (i.e., occupational exposure).[17]

Some evidence has shown a possible risk of active sensitization with *Compositae* mix. In active sensitization, iatrogenic sensitization to a chemical is induced by the application of a patch test. Subsequent patch testing, 10 to 21 days later, detects active sensitization.

Likewise, Kanerva et al reported active sensitization with CM in three patch-tested patients and with SL mix in one patch-tested patient.[18] For this reason, investigative attempts have been made to determine the most ideal supplement for the SL mix that could improve the sensitivity of the test without sensitizing the patient.

Orion et al compared simultaneous patch testing with parthenolide, the feverfew allergen, and SL mix. They reported that supplementation of SL mix with parthenolide did not significantly increase the detection rate. However, in the absence of SL mix, **parthenolide can detect around 75% of SL mix-positive patients**.[19]

Patch testing for specific members of the *Asteraceae* family can be complicated, given the high rate of cross-sensitization among the sesquiterpene lactones. Since SLs have similar chemical structures, the immune system of a patient sensitized to one SL can recognize the structure of another SL, resulting in a positive patch. In fact, when guinea pigs were sensitized with parthenium, cross-reactions with other sesquiterpene lactones were elicited in most study subjects.[20]

Similar cross-reactivities have been noted in 190 *compositae*-allergic patients. For example, if chrysanthemum is a suspected sensitizer, then testing may yield positive reactions to feverfew, tansy, and chamomile tests. In conclusion, this cross-reaction may explain the high prevalence of positive tests.[21]

CURRENTLY AVAILABLE TESTS

The 2007 standard screening tray of the North American Contact Dermatitis Group (NACDG) contains 65 allergen components, which include the CM and SL mixes. Notably, the currently available T.R.U.E. test (Panels 1 and 2) does not include SL mix or CM.

In October of 2005, a partial Panel 3 of the T.R.U.E. test launched in Australia and New Zealand with five additional allergens added to the kit. Seven more allergens will be added to complete Panel 3 and is anticipated for completion in 2008.

ASTERACEAE, COMMONLY KNOWN AS THE DAISY OR SUNFLOWER FAMILY, DERIVES ITS NAME FROM THE GREEK ROOT "ASTER" MEANING "STAR", BECAUSE MANY OF THE FLOWER HEADS OF THESE PLANTS ARE STAR-SHAPED. HOWEVER, UNKNOWN BY MANY PEOPLE, THE ARTICHOKE IS ALSO A MEMBER OF THIS FAMILY.

Due to supply problems, SL mix has not been slated for inclusion, but rather parthenolide will be added because this component detects 75% of SL mix-allergic patients.[22] This update will allow for the use of the T.R.U.E. Test as a screening tool for *Asteraceae* sensitization.

THE VALUE OF THIS PATIENT CASE

The importance of appropriate patch testing with subsequent patient education cannot be understated. With discontinuation of exposure to *Compositae* (avoidance), namely the sunflowers, this patient resolved his pulpitis and remained dermatitis-free.

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