Botanical Briefs: Ginkgo *(Ginkgo biloba)*

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PRACTICE **POINTS**

- Contact with the *Ginkgo biloba* tree can cause allergic contact dermatitis; ingestion can cause systemic dermatitis in a previously sensitized patient.
- *Ginkgo biloba* can cross-react with plants of the family Anacardiaceae, such as poison ivy, poison oak, poison sumac, cashew tree, and mango.
- Ginkgo extract is widely considered safe for use; however, dermatologists should be aware that it can cause systemic dermatitis and serious adverse effects, including internal hemorrhage and convulsions.

Ginkgo biloba is an ancient tree that originated in China and is now cultivated worldwide for its ornamental foliage and resistance to disease and pollution. Direct or indirect interaction with the ginkgo tree can cause allergic contact dermatitis, with erythematous papules, vesicles, and edema on exposed areas due to ginkgolic acids. On the other hand, ginkgo extract, produced from the tree leaves, has long been used in Chinese traditional medicine and is now a popularly consumed herbal medicine. Components of the ginkgo tree can cause dermatitis, but active ingredients in ginkgo extract may be beneficial; research on its safety and potential uses is ongoing.

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An ancient tree of the Ginkgoaceae family, *Ginkgo biloba* is known as a living fossil because its genome has been identified in fossils older than 200 million years.[1] An individual tree can live longer than 1000 years. Originating in China, *G biloba* (here, "ginkgo") is cultivated worldwide for its attractive foliage (Figure 1). Ginkgo extract has long been used in traditional Chinese medicine; however, contact with the plant proper can provoke allergic contact dermatitis.

Dermatitis-Inducing Components

The allergenic component of the ginkgo tree is ginkgolic acid, which is structurally similar to urushiol and anacardic acid.[2,3] This compound can cause a cross-reaction in a person previously sensitized by contact with other plants. Urushiol is found in poison ivy (*Toxicodendron radicans*); anacardic acid is found in the cashew tree (*Anacardium occidentale*). Both plants belong to the family Anacardiaceae, commonly known as the cashew family.

Members of Anacardiaceae are the most common causes of plant-induced allergic contact dermatitis and include the cashew tree, mango tree, poison ivy, poison oak, and poison sumac. These plants can cross-react to cause contact dermatitis (Table).[3] Patch tests have revealed that some individuals who are sensitive to components of

FIGURE 1. *Gingko biloba* can grow to approximately 100 feet.

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Plants That Cross-react With Poison Ivy to Cause Contact Dermatitis

Family	Plant	Allergenic compound	Dermatitis-inducing parts	Habitat
Anacardiaceae	Poison ivy	Urushiol	All	Variety of habitats
	Poison sumac	Urushiol	Fruit and leaves	Wooded, swampy areas
	Cashew tree	Cardol	All except the nut	Tropical regions
	Mango tree	Resorcinols	Leaves, bark, stem, skin of fruit	Tropical and subtropical regions
	Brazilian pepper tree	Various phenols	Sap, crushed berries	Southern Florida
	Japanese lacquer tree	Polymerized urushiol	Sap (used in lacquer)	East Asia
Ginkgoaceae	Ginkgo	Ginkgolic acids	All parts (leaf, stem, fruit)	Worldwide
Proteaceae	*Grevillea* genus	Pentadecylresorcinol	Flower	Australia, Hawaii

the ginkgo tree also demonstrate sensitivity to poison ivy and poison sumac[4,5]; countering this finding, Lepoittevin and colleagues[6] demonstrated in animal studies that there was no cross-reactivity between ginkgo and urushiol, suggesting that patients with a reported cross-reaction might truly have been previously sensitized to both plants. In general, patients who have a history of a reaction to any Anacardiaceae plant should take precautions when handling them.

Therapeutic Benefit of Ginkgo

Ginkgo extract is sold as the herbal supplement EGB761, which acts as an antioxidant.[7] In France, Germany, and China, it is a commonly prescribed herbal medicine.[8] It is purported to support memory and attention; studies have shown improvement in cognition and in involvement with activities of daily living for patients with dementia.[9,10] Ginkgo extract might lessen peripheral vascular disease and cerebral circulatory disease, having been shown in vitro and in animal models to prevent platelet aggregation induced by platelet-activating factor and to stimulate vasodilation by increasing production of nitric oxide.[11,12]

Furthermore, purified ginkgo extract might have beneficial effects on skin. A study in rats showed that when intraperitoneal ginkgo extract was given prior to radiation therapy, 100% of rats receiving placebo developed radiation dermatitis vs 13% of those that received ginkgo extract ($P<.0001$). An excisional skin biopsy showed a decrease in markers of oxidative stress in rats that received ginkgo extract prior to radiation.[7]

A randomized, double-blind clinical trial showed a significant reduction in disease progression in vitiligo patients assigned to receive ginkgo extract orally compared to placebo ($P=.006$).[13] Research for many possible uses of ginkgo extract is ongoing.

Cutaneous Manifestations

Contact with the fruit of the ginkgo tree can induce allergic contact dermatitis,[14] most often as erythematous papules, vesicles, and in some cases edema.[5,15]

Exposures While Picking Berries—In 1939, Bolus[15] reported the case of a patient who presented with edema, erythema, and vesicular lesions involving the hands and face after picking berries from a ginkgo tree. Later, patch testing on this patient, using ginkgo fruit, resulted in burning and stinging that necessitated removal of the patch, suggesting an irritant reaction. This was followed by a vesicular reaction that then developed within 24 hours, which was more consistent with allergy. Similarly, in 1988, a case series of contact dermatitis was reported in 3 patients after gathering ginkgo fruit.[5]

Incidental Exposure While Walking—In 1965, dermatitis broke out in 35 high school students, mainly affecting exposed portions of the leg, after ginkgo fruit fell and its pulp was exposed on a path at their school.[4] Subsequently, patch testing was performed on 29 volunteers—some who had been exposed to ginkgo on that path, others without prior exposure. It was established that testing with ginkgo pulp directly caused an irritant reaction in all students, regardless of prior ginkgo exposure, but all prior ginkgo-exposed students in this study reacted positively to an acetone extract of ginkgo pulp and either poison ivy extract or pentadecylcatechol.[4]

Systemic Contact After Eating Fruit—An illustrative case of dermatitis, stomatitis, and proctitis was reported in a man with history of poison oak contact dermatitis who had eaten fruit from a ginkgo tree, suggesting systemic contact dermatitis. Weeks after resolution of symptoms, he reacted positively to ginkgo fruit and poison ivy extracts on patch testing.[16]

Ginkgo dermatitis tends to resolve upon removal of the inciting agent and application of a topical steroid.[8,17]

Although many reported cases involve the fruit, allergic contact dermatitis can result from exposure to any part of the plant. In a reported case, a woman developed airborne contact dermatitis from working with sarcotesta of the ginkgo plant.[18] Despite wearing rubber gloves, she broke out 1 week after exposure with erythema on the face and arms and severe facial edema.

Ginkgo leaves also can cause allergic contact dermatitis.[19] Precautions should be taken when handling any component of the ginkgo tree.

Oral ginkgo supplementation has been implicated in a variety of other cutaneous reactions—from benign to life-threatening. When the ginkgo allergen concentration is too high within the supplement, as has been noted in some formulations, patients have presented with a diffuse morbilliform eruption within 1 or 2 weeks after taking ginkgo.[20] One patient—who was not taking any other medication—experienced an episode of acute generalized exanthematous pustulosis 48 hours after taking ginkgo.[21] Ingestion of ginkgo extract also has been associated with Stevens-Johnson syndrome.[22-24]

Other Adverse Reactions

The adverse effects of ginkgo supplement vary widely. In addition to dermatitis, ginkgo supplement can cause headaches, palpitations, tachycardia, vasculitis, nausea, and other symptoms.[14]

Metabolic Disturbance—One patient taking ginkgo who died after a seizure was found to have subtherapeutic levels of valproate and phenytoin,[25] which could be due to ginkgo's effect on cytochrome p450 enzyme CYP2C19.[26] Ginkgo interactions with many cytochrome enzymes have been studied for potential drug interactions. Any other direct effects remain variable and controversial.[27,28]

Hemorrhage—Another serious effect associated with taking ginkgo supplements is hemorrhage, often in conjunction with warfarin[14]; however, a meta-analysis indicated that ginkgo generally does not increase the risk of bleeding.[29] Other studies have shown that taking ginkgo with warfarin showed no difference in clotting status, and ginkgo with aspirin resulted in no clinically significant difference in bruising, bleeding, or platelet function in an analysis over a period of 1 month.[30,31] These findings notwithstanding, pregnant women, surgical patients, and those taking a blood thinner are advised as a general precaution not to take ginkgo extract.

Carcinogenesis—Ginkgo extract has antioxidant properties, but there is evidence that it might act as a carcinogen. An animal study reported by the US National Toxicology Program found that ginkgo induced mutagenic activity in the liver, thyroid, and nose of mice and rats. Over time, rodent liver underwent changes consistent with hepatic enzyme induction.[32] More research is needed to clarify the role of ginkgo in this process.

Toxicity by Ingestion—Ginkgo seeds can cause food poisoning due to the compound 4′-O-methylpyridoxine (also known as ginkgotoxin).[33] Because methylpyridoxine can cause depletion of pyridoxal phosphate (a form of vitamin B_6 necessary for the synthesis of γ-aminobutyric acid), overconsumption of ginkgo seeds, even when fully cooked, might result in convulsions and even death.[33]

Nomenclature and Distribution of Plants

Gingko biloba belongs to the Ginkgoaceae family (class Ginkgophytes). The tree originated in China but might no longer exist in a truly wild form. It is grown worldwide for its beauty and longevity. The female ginkgo tree is a gymnosperm, producing fruit with seeds that are not coated by an ovary wall[15]; male (nonfruiting) trees are preferentially planted because the fruit is surrounded by a pulp that, when dropped, emits a sour smell described variously as rancid butter, vomit, or excrement.[5]

Identifying Features and Plant Facts

The deciduous ginkgo tree has unique fan-shaped leaves and is cultivated for its beauty and resistance to disease (Figure 2).[4,34] It is nicknamed the maidenhair tree because the leaves are similar to the pinnae of the maidenhair fern.[34] Because *G biloba* is resistant to pollution, it often is planted along city streets.[17] The leaf—5- to 8-cm wide and a symbol of the city of Tokyo, Japan[34]—grows in

FIGURE 2. Fan-shaped leaves of the ginkgo tree.

FIGURE 3. Ginkgo leaves in clusters of 3 to 5.

clusters (Figure 3)[5] and is green but turns yellow before it falls in autumn.[34] Leaf veins branch out into the blade without anastomosing.[34]

Male flowers grow in a catkinlike pattern; female flowers grow on long stems.[5] The fruit is small, dark, and shriveled, with a hint of silver[4]; it typically is 2 to 2.5 cm in diameter and contains the ginkgo nut or seed. The kernel of the ginkgo nut is edible when roasted and is used in traditional Chinese and Japanese cuisine as a dish served on special occasions in autumn.[33]

Final Thoughts

Given that *G biloba* is a beautiful, commonly planted ornamental tree, gardeners and landscapers should be aware of the risk for allergic contact dermatitis and use proper protection. Dermatologists should be aware of its cross-reactivity with other common plants such as poison ivy and poison oak to help patients identify the cause of their reactions and avoid the inciting agent. Because ginkgo extract also can cause a cutaneous reaction or interact with other medications, providers should remember to take a thorough medication history that includes herbal medicines and supplements.

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