

The major allergen of *Dendropanax trifidus* Makino

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Dendropanax trifidus Makino (family Araliaceae, syn. *Gilibertia trifida* Makino) has been reported as causing allergic contact dermatitis in Japan. To identify the major allergen, fractionated extracts of fresh leaves of *Dendropanax trifidus* were patch tested on 2 patients with hypersensitivity to the plant. Cis-9,17-octadecadiene-12,14-diyne-1,16-diol (**I**), an analog of faltarinol, was identified as an active component. 18 normal control subjects were patch tested with the leaf of *Dendropanax trifidus* and **I** diluted to 0.05% in pet. 4 of them showed active sensitization to the leaf of *Dendropanax trifidus* and **I**. Our results suggest that **I** is the major allergen of *Dendropanax trifidus* and is a strong sensitizer. The results of patch testing on patients and control subjects with the leaves of *Fatsia japonica* Decne. et Planch. and *Hedera helix* L., which also belong to the Araliaceae family, and urushiol are also shown.

Key words: phytocontact allergy; *Dendropanax trifidus*; cis-9, 17-octadecadiene-12, 14-diyne-1, 16-diol; cross-reaction; *Fatsia japonica*; *Hedera helix*; faltarinol; plants; active sensitization. © Munksgaard, 1997.

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The genus *Dendropanax*, belonging to the family Araliaceae, can be found distributed in East Asia, the Malay peninsula, and Central and South America. Although there are more than 30 species, *Dendropanax trifidus* Makino (1, 2) is the only one found in Japan. It is a ubiquitous evergreen plant found in the west of the Kanto region of Japan. The plant is commonly cultivated in gardens and sometimes used for flower arrangements. The stem is erect and can grow to a height of 5 m. The leaves are 3-lobed and glossy green in color (Fig. 1). The Japanese name for the plant is *kakuremino*, because the leaves of the plant resemble the *kakuremino*, or Japanese straw coat.

After pruning or arranging the branches and leaves of the plant, some people develop contact dermatitis (3-6). However, the actual components of *Dendropanax trifidus* that cause allergic contact dermatitis are not yet known. In the first report of contact dermatitis due to *Dendropanax trifidus* (3), cross-reaction with urushiol was suggested. In other reports, cross-reactions with *Fatsia japonica* Decne. et Planch. which also belongs to the family Araliaceae and is a popular and native plant in

Japan, have been reported (4-6). In this report, we describe the identification of a contact allergen in *Dendropanax trifidus* and the investigation of the cross-reactions with other plants.

Materials, Methods and Results

Identification of an allergen from *Dendropanax trifidus*

Patients. The 2 patients are also 2 of the authors of this paper. Case no. 1 is a 75-year-old man with a previous history of contact dermatitis due to *Dendropanax trifidus*, *Primula obconica*, *Toxicodendron verniciflua*, ginkgo fruit, wool wax alcohols, and hydrogenated lanolin. Case no. 2 is a 43-year-old woman with no previous history of contact dermatitis before she began investigating *Dendropanax trifidus* in September 1993. After pruning the leaves of *Dendropanax trifidus* on the morning of 11 July 1994, she developed acute dermatitis on the hands, arms, cheeks, neck and chin by the next morning. On patch testing, these 2 patients both showed strong positive reactions to the leaf of *Dendropanax trifidus*.



Fig. 1. *Dendropanax trifidus* Makino.

Isolation of allergen from *Dendropanax trifidus*. 330 g of fresh leaves of *Dendropanax trifidus* were soaked in 3 l of 80% methanol for 1 week and the extract concentrated under reduced pressure to 1/10. The concentrate was extracted with CHCl_3 and H_2O . The organic layer was evaporated to dryness. The residue was then extracted with 70% methanol to remove insoluble tar substances. The 70% methanol soluble fraction was roughly separated into 29 fractions by ODS column chromatography, with methanol-water gradient elution from 60% to 80% and acetonitrile, and then concentrated under reduced pressure. The fractions were diluted in white petrolatum for patch testing.

Patch testing with 29 fractions and their results. The 29 fractions were used for patch testing on the 2 patients. Test samples were applied on the flexor side of the upper arm, using Finn Chambers® (Epitest Ltd., Helsinki, Finland) and Scanpor® tape (Norgesplaster A/S, Oslo, Norway). The reactions were read at 2, 3 and 7 days according to the ICDRG classification. The patients showed positive reactions to 2 out of the 29 fractions.

Purification and analysis of allergens. The 2 fractions responsible for the positive reactions were purified 3× under several conditions by ODS column chromatography, and 2 compounds suspected

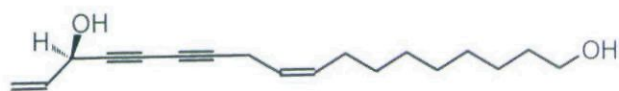


Fig. 2. Structure of cis-9,17-octadecadiene-12,14-diyne-1,16-diol (I).

as allergens were extracted. ^1H NMR and ^{13}C NMR analyses and HR mass spectrometry indicated that one of the compounds was cis-9,17-octadecadiene-12,14-diyne-1,16-diol (I) (Fig. 2), which is the hydroxymethyl derivative of falcarinol. When patch tested with I diluted to 0.05% in pet., the 2 patients again showed strong positive reactions.

Evaluation of the allergenicity of I and cross-reactivity

Patch testing on patients. To investigate cross-reactivity, patch testing was performed on the 2 patients with the leaves of *Fatsia japonica*, *Hedera helix* L. and 0.01% urushiol (Torii Pharmaceutical Co., Ltd. Tokyo, Japan). Both patients showed positive reactions to the leaf of *Fatsia japonica*. Case no. 1 also showed positive reactions to the leaf of *Hedera helix* L. and 0.01% urushiol (Table 1).

Patch testing on control subjects. 18 healthy subjects aged between 24 and 43 years participated in this study, 13 male and 5 female. None of them had any previous history of contact dermatitis due to *Dendropanax trifidus*. 3 of them, however, had a previous history of *Rhus* dermatitis. Prior to the experiment, informed consent was obtained from all participants.

The participants were patch tested with the leaf of *Dendropanax trifidus*, leaf of *Fatsia japonica*, I 0.05% pet. and urushiol 0.01%. Readings were made as described before.

5 subjects (Case nos. 3–7) showed irritant reactions to the leaf of *Dendropanax trifidus*, and 4 out of the 5 (Case nos. 3–6) showed flare-up reactions at the patch test sites 9 to 11 days later. The same subjects also showed flare-up reactions to I. 2 (Case nos. 3 and 6) out of the 4 also showed flare-

Table 1 Results of patch testing

Case no.	1	2	3	4	5	6	7
<i>Dendropanax trifidus</i>	+	++	IR,FU	IR,FU	IR,FU	IR,FU	IR
<i>Fatsia japonica</i>	+	+	IR,FU	—	IR	FU	IR
<i>Hedera helix</i>	+	—	NT	NT	NT	NT	NT
I 0.05% pet.	++	++	FU	FU	FU	FU	—
urushiol 0.01% pet.	+	—	++	—	+	++	—

Case nos. 1 and 2: patients.

Case nos. 3–7: control subjects who reacted on patch testing. IR: irritant reaction. FU: flare-up reactions. NT: not tested.

up reactions at sites patch tested with the leaf of *Fatsia japonica* (Table 1). The 3 subjects (Case nos. 3, 5 and 6) with a previous history of *Rhus* dermatitis also showed positive reactions to urushiol. The other 13 subjects showed no reaction.

Discussion

Contact dermatitis due to *Dendropanax trifidus* was first reported in 1975 (3) and cross-reaction with urushiol was then suggested. Saito et al. (4, 5) subsequently reported 7 patients with contact dermatitis due to *Dendropanax trifidus*. In their reports, 2 of the 7 patients also had a previous history of contact dermatitis due to *Fatsia japonica* (Araliaceae family), and the authors suggested that the 2 plants might have the same or cross-reacting allergens. Of the 7, 5 patients reacted positively when patch tested with an ethanol extract of the leaves of *Fatsia japonica*. Again, among the 7 patients, 3 showed strong positive reactions when patch tested with 0.01% urushiol. In their reports, Saito et al. (5) demonstrated by TLC analysis that in the ethanol extract of the leaves of *Dendropanax trifidus*, there was a spot compatible with urushiol and suggested that urushiol might be present in *Dendropanax trifidus*. However, they did not purify the spot to investigate further. On the other hand, the ethanol extract of *Fatsia japonica* did not show the same spot as that of urushiol.

In another report (6), 1 of 2 patients patch tested with the leaf saps of *Dendropanax trifidus*, *Fatsia japonica* and 0.002% urushiol showed positive reactions to the leaf saps of the 2 plants but no reaction to urushiol. In the same report, 6 normal control subjects were patch tested with the leaf sap of *Dendropanax trifidus* but only 1 of them showed a flare-up reaction 7 days later. In other words, although cross-reactions between *Dendropanax trifidus*, *Fatsia japonica* and urushiol had been studied before, the facts remained controversial.

In the present study, our results demonstrated that 2 patients (Case nos. 1 and 2) with dermatitis due to *Dendropanax trifidus* reacted strongly to **I** on patch testing and 4 (Case nos. 3–6) out of 18 control subjects (22%) were actively sensitized to the leaf of the plant and **I**. We can therefore confirm that **I** is the major allergen of *Dendropanax trifidus* and a strong sensitizer. The constituents of another fraction, which also elicited reactions on the 2 patients, are considered to contain compounds analogous to **I**. However, we were unable to identify these constituents because of difficulty in purifying this fraction as its quantity in each sample was inconsistent. This inconsistency could perhaps have been due to seasonal or regional fac-

tors, depending on when or where the leaves were gathered. The amount of **I**, however, was constant and did not vary among samples.

I was first purified and analyzed from *Dendropanax trifidus* in 1973 (7) and reported as an antifungal agent. Some other compounds, such as dendropanaxide, friedelin, epifriedelinol, β -amyrin and β -sitosteryl- β -D-glucoside, have also been identified as components of *Dendropanax trifidus* (8), but their allergenicity is not known.

In chemotaxonomy and pharmacology, polyacetlenes in the Araliaceae family have been studied and isolated (9). In 1964, falcarinol was isolated from *Panax ginseng* C. A. Meyer (10). Falcarinol isolated from *Hedera helix* L., *Hedera canariensis* (11), and *Schefflera arboricola* (12) was also identified as the major allergen of those plants. Falcarinol is thought to function as an alkylating agent (13). As the chemical structure of **I** is closely related to falcarinol, it is supposed that **I** also acts as an alkylating agent on protein, resulting in the formation of haptens.

In our experiments, the 2 patients had positive responses to the leaf of *Fatsia japonica* when patch tested. 2 control subjects (Case nos. 3 and 6), after being actively sensitized to *Dendropanax trifidus* and **I**, also showed flare-up reactions when patch-tested with the leaf of *Fatsia japonica*, supporting previous findings (4–6) that the same or cross-reacting agents are found in the 2 plants. On the other hand, when patch tested, Case no. 1 also showed a positive reaction to *Hedera helix* L. A similar case of positive patch test reactions to certain other plants of the Araliaceae family had previously been reported (14). However, the major allergen of *Hedera helix* L. is falcarinol and falcarinol has been reported to be absent in *Fatsia japonica* (13). Further studies are necessary to evaluate the allergen in *Fatsia japonica* and to investigate whether cross-reacting agents are present among plants belonging to the Araliaceae family.

In the present study, 3 (Case nos. 3, 5 and 6) out of 4 control subjects actively sensitized with *Dendropanax trifidus* and **I** had previous histories of *Rhus* dermatitis, and also demonstrated positive reactions to urushiol. Concomitant dermatitis due to 2 plants belonging to Anacardiaceae family and Araliaceae family has also been reported outside Japan (15, 16). However, when 4 other patients (not among the control subjects) with *Rhus* dermatitis were patch tested with urushiol and **I**, they all showed positive reactions to urushiol and negative reactions to **I** (data not shown). This suggests that urushiol does not cross-react with **I**. We can therefore assume either that the positive reaction to urushiol and the sensitization to *Dendropanax trifidus* and **I** in our 3 control subjects was coincidental, or

that people sensitized with urushiol are more apt to be sensitized to plants of the Araliaceae family.

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