

A study of cross-reactions between mango contact allergens and urushiol

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The allergens causing mango dermatitis have long been suspected to be alk(en)yl catechols and/or alk(en)yl resorcinols on the basis of observed cross-sensitivity reactions to mango in patients known to be sensitive to poison ivy and oak (*Toxicodendron* spp.). Earlier, we reported the 3 resorcinol derivatives: heptadecadienylresorcinol (I), heptadecenylresorcinol (II) and pentadecylresorcinol (III); collectively named 'mangol', as mango allergens. In this study, we extracted the 1st 2 components (I and II) from the Philippine mango, adjusted them to 0.05% concentration in petrolatum and patch tested the components on 2 subjects with mango dermatitis. Both subjects reacted to I. 1 subject also elicited a weaker positive reaction to II. To investigate the cross-reaction between mangol and urushiol, we also patch tested the same subjects with urushiol. The subject sensitive to II reacted to urushiol. 6 subjects with a history of lacquer contact dermatitis and positive reactions to urushiol were similarly patch tested. 5 persons reacted to I. 2 subjects also exhibited a slower but positive reaction to II. This is the 1st report in which heptadec(adi)enyl resorcinols known to be present in mango have been shown to elicit positive patch test reactions in mango-sensitive patients.

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The mango, scientific name *Mangifera indica* L. (fam. Anacardiaceae), is known as 'the king of fruits'. Its origins are in eastern India, but today the fruit is widely grown and produced in many tropical areas (1). In Japan, mango was an imported fruit, but it is now cultivated in the southern parts of Japan. People develop allergic contact dermatitis after peeling and eating mangoes. The mango allergens, named collectively as 'mangol' in our previous article (2), have been identified as a mixture of alk(en)yl resorcinols analogous to cardol (3–5), but otherwise there are few detailed reports on mango allergens.

Contact dermatitis due to urushi or lacquer, derived from other members of the Anacardiaceae family, constitutes more than half of plant contact dermatitis seen among the outpatients in our clinic. Urushi here refers to the 5 species found in Japan (6) *Toxicodendron vernicifluum* F. Barkley (Japanese lacquer tree), *T. sylvestre* Kuntze, *T. succedaneum* Kuntze (Japanese wax tree), *T. orientale* Greene and *T. trichocarpum*

Kuntze. Because mango also belongs to the Anacardiaceae family, it is only natural to assume that patients who have a history of lacquer dermatitis also have a tendency to develop mango dermatitis.

Our previous report in 1994 was on mango allergens (2). In that study, we patch tested 3 subjects with a history of mango dermatitis with fractions extracted from the Philippine mango to determine the fraction that contained the allergens. All 3 subjects reacted to the fraction containing alk(en)yl resorcinol components but did not react to β -pinene or limonene, which were also thought to be potential allergens of mango (1). The components, which we named 'mangol', were heptadecadienylresorcinol (I), heptadecenylresorcinol (II) and pentadecylresorcinol (III).

In this study, we used the same method to extract and refine the 1st 2 alkylresorcinol components and patch tested them to confirm that the 2 components are indeed the mango

allergens. We also studied the cross-sensitivity between mango allergens and urushiol.

Materials, Methods and Results

Patients

2 patients with a previous history of mango dermatitis but no history of urushi dermatitis participated in this study. Case no. 1 is a 25-year-old woman who developed mango dermatitis 5 years ago. On this occasion, she experienced an irritation of the lower lip the day after she peeled and ate some mangoes (*Carabao* variety). The skin lesions worsened and spread to other parts of her face. When she consulted us on the 5th day, there was erythema and swelling around the eyes, and an erythematous papular reaction around the lips, the left ear lobe and on the right hand. Case no. 2 is a 27-year-old woman. She had started eating mangoes presented to her as a gift from Okinawa, Japan (*Irwin* variety). On the 9th day, she started to experience a stinging sensation on her lips but nevertheless continued to eat the mangoes. She consulted our clinic 2 days later when her symptoms deteriorated. When examined, she had erythematous lesions with vesicles on her lower lip, chin and neck.

In addition, 6 subjects with a history of urushi dermatitis but without any history of mango dermatitis also participated in this study. They were 5 males aged 71, 67, 74, 53 and 21, and a 65-year-old female. The first 3 subjects developed contact dermatitis from urushi after pruning or cutting the branches of *T. succedaneum* in their gardens. The other 3 subjects developed urushi dermatitis

after touching the sap of urushi plants (either *T. orientale* or *T. sylvestris*) during a mountain hike.

Isolation of allergens from mango

Fresh epicarp of the Philippine mango (*Carabao* variety) was soaked in EtOH for 1 month. After decantation, the EtOH solution was evaporated to dryness. The tar residue (2.7 g) was dissolved with 15 ml of CHCl_3 and was fractionated by column chromatography on silica gel (Wakogel C200; 100 g) with CHCl_3 and CHCl_3 -AcOEt (1:1). The fraction eluted from the latter solvent was concentrated under reduced pressure and was dissolved with 4.0 ml of 80% CH_3CN -0.01N HCl solution for high-performance liquid chromatography (HPLC) analysis. 8 fractions were obtained by HPLC (Fig. 1). By comparing with our previous data, Fr2 to Fr4 were estimated as the fractions that contained the mangol allergens. Further purification of these fractions was performed by HPLC using 1 ml of the prepared sample. Isolation of Fr2–Fr4 was carried out as follows: The column was TSK ODS80TM (6 mm $\times$ 150 mm), kept at 40°C and eluted with a 25 min linear gradient from 80% to 100% acetonitrile-0.01N HCl solution. Fr2–Fr4 (detected by measuring absorbance at 275 nm) were collected and lyophilized. The yield of each fraction was as follows: Fr2 = 2.5 mg, Fr3 = 0.8 mg and Fr4 = 3.9 mg.

The structures of each fraction were determined by spectroscopic analysis. ^1H -NMR, ^{13}C -NMR analyses and mass spectroscopy indicated that Fr2 was 5-(9Z,12Z-heptadecadienyl)-resorcinol (I)

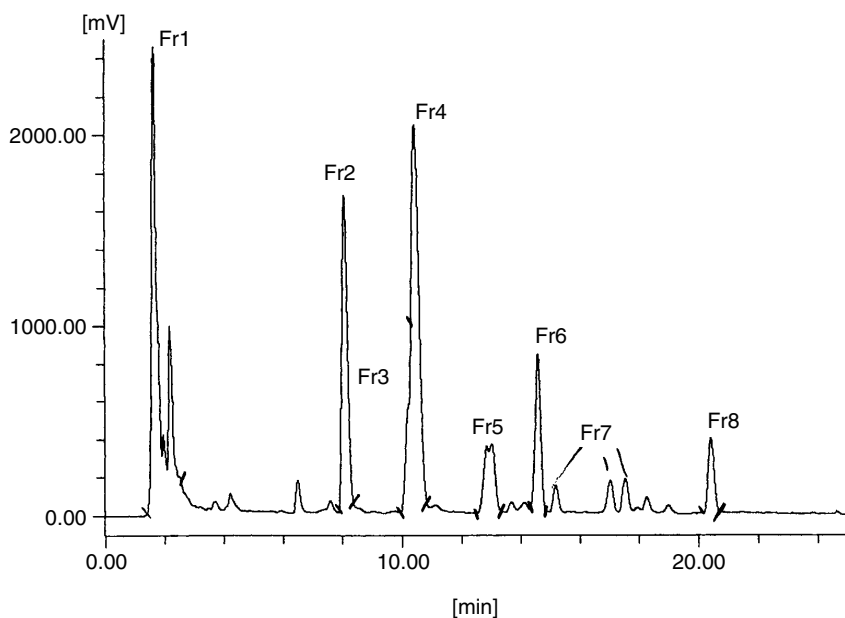


Fig. 1. The chromatogram of mangol.

and Fr4 was 5-(12Z-heptadecenyl)-resorcinol (II) (Fig. 2). Fr3 was presumed to be a mixture of palmitic acid, 5-pentadecylresorcinol (III) and II in a ratio of 4:3:2. More detailed analysis of the structural determination of mangol will be reported separately.

Patch testing

Patch test samples were 0.05% I and 0.05% II in petrolatum (pet.), and 0.01% urushiol (Torii Pharmaceutical Co., Ltd. Tokyo, Japan), the allergens of urushi lacquer. The samples were applied on the flexor side of the upper arm, using Finn Chambers[®] (Epitest Ltd, Helsinki, Finland) on Scanpor[®] (Norgesplaster A/S, Oslo, Norway) tape. Reactions were read on day 2 and day 3 or day 4 according to the ICDRG classification. 10 healthy control volunteers having no history of mango dermatitis or urushi dermatitis were similarly patch tested with the same samples and none showed any positive reactions.

Results of patch testing

The 2 subjects with mango dermatitis (Case nos. 1 and 2) reacted to I (Table 1). Case no. 1 also elicited a weaker positive reaction to II and to urushiol, whereas 5 of 6 subjects with urushi dermatitis reacted positively to urushiol and I. 2 subjects with urushi dermatitis showed a slower but nevertheless positive reaction to II.

Discussion

The allergens of mango have long been thought to be substances similar to cardol, the main allergen found in cashewnut oil, which belongs to the same plant family (1, 3–5), though this had never been confirmed. Benezra et al. (1985) (1) suggested that β -pinene and limonene contained in mango could be the allergens. In 1994, we patch tested 3 subjects with mango dermatitis using the extracts from mango epicarp and clearly demonstrated that mango allergens were 5-alkenyl resorcinols. The main components, I and II, have 17 carbons in the side chain of 5-alkenyl resorcinols,

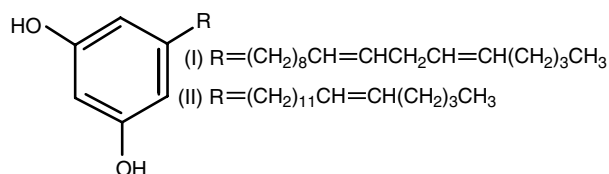


Fig. 2. Chemical structure of mangol I(5-(9Z,12Z-heptadecadienyl)-resorcinol) and II(5-(12Z-heptadecenyl)-resorcinol).

Table 1. Results of patch testing (ICDRG classification)

Past history	Mango dermatitis				Urushiol Urushi dermatitis							
Case number	1	2	3	4	5	6	7	8				
Day	2	3	2	4	2	3	2	3	2	3	2	3
I (0.05%)	+	++	-	+	+	+	+	+	+	+	-	-
II (0.05%)	+	+	-	-	-	+	-	-	-	-	+	-
Urushiol (0.01%)	+	++	-	-	+	+	+	+	+	+	+	+

compared with 15 carbons in cardol. The 3 allergens were collectively called mangol and were found present in percentages of 35.5%, 56.6% and 7.9%, respectively (2).

In this study, we extracted and refined the alkenyl resorcinols from the epicarp of Philippine mango, *Carabao* variety, and determined their chemical structures. II was 5-(12Z-heptadecenyl)-resorcinol, with the same chemical structure as the compound having antibacterial properties reported by Cojocar et al. (7), while the component reported as mango latex (8) has the same molecular weight, but the position of the unsaturated bond was different. I was 5-(9Z,12Z-heptadecadienyl)-resorcinol and a new finding as far as we know. Further details of the chemical structures of these components will be reported separately.

On this occasion, we were able to extract the mangol components in the following proportions: 38% for I and 62% for II. The ratio of I to II was similar to our previous report (2), but we were unable to extract a significant amount of III this time. We do not know the reason for this, but the mango variety and the degree of ripening of the fruit may be reasonable and possible explanations for the varying amounts of I, II and III extracted each time. Many past studies did not identify the mango species used, making it difficult to make comparisons.

Mango is a tropical fruit that is not indigenous to Japan, but in 1943, Asai (9) first reported 26 cases of mango dermatitis in Taiwan, which was then Japanese territory. Years later, Japan imported mangoes from the Philippines and Mexico, and in recent years has even begun cultivating mangoes in the warmer parts of its archipelago such as Okinawa and the southern parts of Kyushu, and today, mango dermatitis is not uncommon in Japan.

Urushi or lacquer dermatitis is commonly seen in Japan because patients develop urushi dermatitis when they inadvertently come into contact with lacquer plants in their own garden or while on a mountain hike, or after using a pair of newly

lacquered chopsticks! In fact, urushi is an important cause of plant dermatitis in Japan (10). In autumn, patients develop contact dermatitis from ginkgo nuts when they come into contact with the skin either while picking the nuts or while removing the skin itself from the nuts (11).

The allergens in urushi are alkylcatechols, identified as 3-pentadecylcatechol, monoolefin, diolefin and triolefin with 15 carbons in their side chains (4, 12). The tester, 0.01% urushiol (Torii®) used in this study for patch testing is thought to contain a mixture of these catechols (13). Ginkgo nuts possess components similar to cashew nuts (14). Because the chemical structures of allergens belonging to the Anacardiaceae family and the Ginkgoaceae family are alkyl or alkenyl catechols and alkyl or alkenyl resorcinols, the alkyl or alkenyl group might be recognized as an epitope and the latter are thought to act as common allergens (15).

Cross hypersensitivity between the allergens of these plants had been known, and Asai (9) in his report mentioned that of the 20 patients with mango dermatitis, 8 of them also had a history of lacquer dermatitis. When Keil et al. (3) patch tested 3-n-pentadecylcatechol (PDC), as the allergen of poison ivy, and mango stem sap on 39 subjects who had no previous contact with the fruit, he observed that 66% of the subjects who were positive to PDC were also sensitive to mango stem sap. In our previous report (2), we patch tested 14 subjects with mango dermatitis with mango, ginkgo nuts, urushiol and found that all subjects reacted positively to the 50% mango extract and ginkgo-alcohol extract and only 7 subjects (50%) reacted positively to 0.01% urushiol in pet. Whereas urushiol is a catechol derivative, ginkgo nuts contain a resorcinol derivative known as bilobol not dissimilar to mangol; and therefore cross-reaction between the latter two is more likely.

We had 2 subjects with mango dermatitis; Case no.1 was caused by the *Carabao* variety and Case no. 2 by the *Irwin* variety. Although the concentration of II is twice that of I in the natural fruit when adjusted to 0.05% concentration in pet. and patch tested, Case no. 1 elicited a strong positive reaction to I and a positive reaction to II, but Case no. 2 elicited a positive response only to I. This indicated that diolefin (I) has a much stronger allergenicity compared with monoolefin (II). In similar studies on the allergenicity of poison ivy urushiol (12), the allergenicity of the component is said to depend on the number of side chain double bonds in the third position of catechols; in other words, like mangol, diolefin is more allergenic than monoolefin in urushiol.

There are indeed few comparative studies on the cross-sensitivity of resorcinols and catechols derived from plants. When 38 subjects with poison ivy dermatitis were patch tested with cardol and its related substances, including anacardic acid, anacardol and tetrahydrocardol, and their cross-reactivity compared, 0.01% cardol, which is an alkylresorcinol, elicited a strong positive reaction (16). In another clinical study, 5-(8Z, 11Z-heptadecadienyl) resorcinol, the allergen of *Philodendron* species which is indigenous to Hawaii, was extracted and patch tested simultaneously with urushiol on patients, and cross-sensitivity between catechol and resorcinol did not occur (17, 18).

In this study, we found that even though both subjects with mango dermatitis had no previous history of urushi sensitivity, 1 of them nevertheless reacted positively when patch tested with 0.01% urushiol. On the other hand, 5 of 6 subjects (83%) with no history of mango dermatitis reacted positively to I and 2 (33%) of them to II. This study clearly demonstrated that cross-sensitivity exists between urushiol and mangol among patients with either mango or lacquer dermatitis.

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