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REVIEW ARTICLE

Recent Advances in Research on Lacquer Allergy

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ABSTRACT
Allergic contact dermatitis caused by contact with lacquer sap and lacquerware affects the welfare of lacquer workers and the lacquerware industry. Many studies of the mechanism of urushiol allergy, including animal models, have been carried out and have established several hypotheses. In order to provide a comprehensive understanding of lacquer allergy, we review recent advances in the research on lacquer allergy including the chemical properties of lacquer lipid components, allergic mechanism analyses, immunological explanations, allergy medications, and the prevention combined with the research results from our laboratory.

KEY WORDS
lacquer allergy, lacquer sap, lacquerware, urushiol

INTRODUCTION

Lacquer is a natural polymer collected from lacquer trees; it has durability and beauty and has been used in Asia for a thousand years.[1-5] Lacquer was first used as an adhesive for fixing gold foil, chipped porcelain, or attaching arrowheads to the wooden shaft. Then, with the accumulation of experience and awareness, lacquer was applied to bamboo, wood, and other furniture. It is still used in daily life in crafts and industrial equipment. Collecting lacquer sap is like collecting gum from a rubber tree. The bark of the lacquer tree is tapped and the milky-white saps exude collected. The sap of lacquer is collected from the 5- to 10-year-old lacquer trees between June and October. The sap obtained is an emulsion of water in oil, which is called raw lacquer. After being stirred to homogenize it and heated to evaporate the water, fine lacquer, also called *kurome* lacquer in Japanese, is produced.

In Asian countries, lacquer sap is obtained mainly from the lacquer trees of *Rhus vernicifera* in China, Japan, and Korea, *Rhus succedanea* in Vietnam and Taiwan, and *Melanorrhoea usitata* in Myanmar and Thailand. The constituents and properties of the lacquers differ not only with the species but also with the age of trees, place grown, and season of collection. The constituents are lipid components (60-70%), water (20-30%), plant gum (4-10%), the enzyme laccase (1.5-2%), and water-insoluble glycoprotein (3-5%).[6]

Early in 1922, a Japanese researcher, Majima, sketched the skeleton of urushiol, a dihydric phenol with a side chain of 15 carbon atoms and suggested that at least three similar compounds were also present, with one, two, or three double bonds in the side chain.[7] Further studies revealed that some of the side chains can contain up to 17 carbon atoms, and that the double bonds may occur in a variety of positions. The nucleus may also differ, both in the position and the number of side groups with at least two forms of a monohydric phenol having been detected.[8]

Lacquer has been studied in our laboratory for over thirty years. Fast drying,[9] hybrid,[10,11] nano,[12] and synthetic lacquers[13] have been examined in detail. The deterioration and restoration of lacquer film,[14] structural analysis of lipid components of lacquers,[15] and enzymatic dehydrogenative polymerization[16] have also been reported. The comprehensive results of lacquer research performed so far on the structures of lipid compositions of oriental lacquer saps are summarized in Table 1.

Because the main component of lacquer has a catechol ring structure, it caused dermatitis in lacquer workers.[17-19] Therefore, studies of the external manifestations, results, allergic mechanism, medical treatment, and prevention have been ongoing. This review is to reveal the recent advances in the re-

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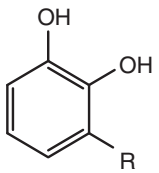
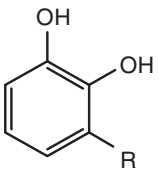
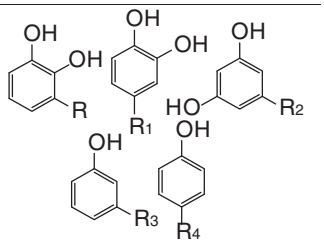
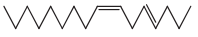
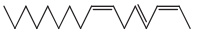
Table 1 Components and structures of Oriental lacquer saps

Rhus vernicifera		*Rhus succedanea*		*Melanorrhoea usitata*	
Urushiol		Laccol		Thitsiol	
					
C_{15}	%	C_{15}	%		%
R =	4.5	R =	1.3	R =	3.9
	15.0	C_{17}			7.5
	1.5		54.9		0.35
	4.4		4.9		36.0
	6.5		15.6	R_1 =	
	55.4		1.9		0.73
	1.7		17.2		20.0
	7.4		2.4		20.6
C_{17}			1.8		0.73
	1.5				1.13
	1.8				3.63
Unidentified components	0.3			R_2 =	
					0.69
					2.1
				R_3 =	1.38
				R_4 =	1.03
				Unidentified components	0.23

search of lacquer allergy including urushiol haptens, allergic mechanism analysis, immunological explanation, allergic medication, and the prevention.

MECHANISM OF LACQUER ALLERGY

Lacquer allergy usually refers to the allergic contact dermatitis that caused by the lipid components contained in lacquer sap. The lacquer lipid component is a hapten from the viewpoint of immunology.[20] It is generally believed that the *O*-quinones derived from the oxidation of urushiols are susceptible to nucleophilic attack at the catechol ring in positions 4, 5, and 6 by proteins to form a complete antigen.[21] The mechanism of allergic contact dermatitis has been evolved considerably by Polak[22] and Benezra *et al*.,[23] respectively.

The cellular events of lacquer allergy can be divided into induction and elicitation phases. In the induction phase, the hapten penetrates the skin and becomes a protein-hapten complex as a complete antigen, which can be incorporated into Langerhans cells (internalization) and present antigen information to T lymphocytes. These T lymphocytes then migrate to the lymph nodes where they differentiate and proliferate into *effector* cells and *memory* cells. At this point, the individual is hypersensitive and has immunologically prepared T lymphocytes that can react to a later attack by the same hapten.

In the elicitation phase, the hapten once again comes into contact with the skin and the previously formed protein-hapten complex. The effecter cells that were formed during the first contact and circulate in the blood now come into contact with the complex. These effector cells release chemical mediators called cytokines whose properties have been studied extensively.[24] Cytokines are aimed at different targets: macrophages, lymphocytes, and other cell types (cytotoxic for T cells particular). These cytokines are responsible for the pathologic manifestations of allergic contact dermatitis, erythema, papules, vesicles,

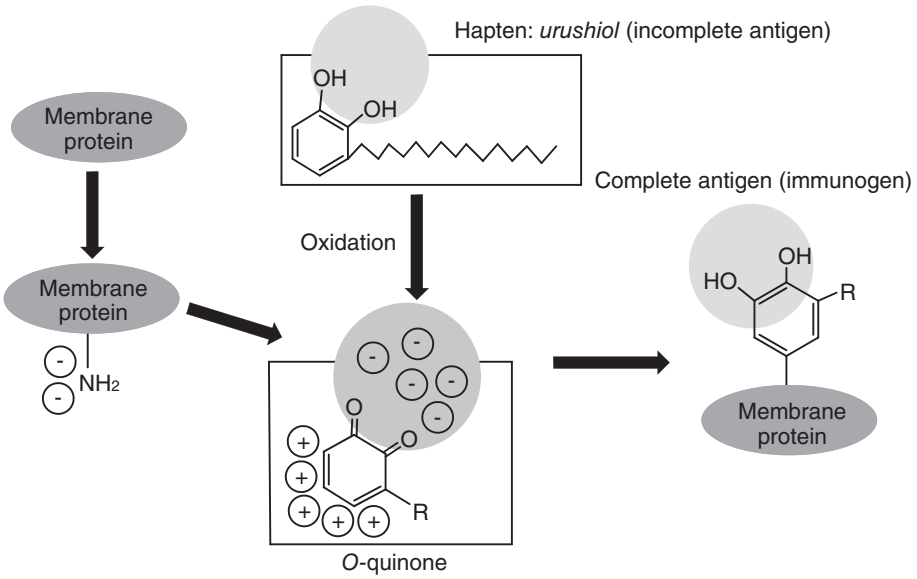


Fig. 1 Mechanism of urushiol allergy.

and/or swelling.[25,26]

In the case of lacquer, the lipid components of lacquer urushiol, laccol, and thitsiol, are not electrophiles and can not react with electrophilic proteins to form an antigen.[21] When these lipid molecules penetrate the skin, an enzyme catalyzes oxidation reaction and converts the lipids into *O*-quinones, which are authentic electrophiles, and react to keratin or protein in the cellular membrane to form a complete antigen, as shown in Figure 1. This urushiol antigen is captured by Langerhans cells, presents antigen information to T lymphocytes, and induces sensitization of T cells. In the initial sensitization process, while interleukin-1β (IL-1β) is produced by Langerhans cells, major histocompatibility complex (MHC) class II is expressed on the cell surface of Langerhans cells and recognized by T cells via T cells receptor (TCR) together with antigen fragments.[27] The keratinocytes produce urushiol-generated cytokines such as tumor necrosis factor α (TNF-α), IL-1α, and granulocyte/macrophage colony-stimulating factor (GM-CSF), which further activates the Langerhans cells.[28] After establishment of sensitization to urushiol, contact dermatitis occurs with the re-invasion of urushiol antigen, as shown in Figure 2. On the other hand, sometimes when the MHC class II presents antigen information to T lymphocytes, T cells does not react to the same antigen as they should, which is called "anergy", and this phenomenon is considered to be desensitization or hyposensitization. Watanabe *et al*.[29] have showed that, in mice, inflammasome-signaling level can be modulated to turn dinitrothiocyanobenzene into a sensitizer and dinitrofluorobenzene into a tolerizer, and this is correlated with Th1, Th17, and regulatory T cells. The feature of lacquer allergy is that with the increased exposure experience to lacquer sap, the symptoms gradually relieved. The reason may be considered due to the regulatory T cells, and affecting the balance of Th1 and Th2.

IMMUNOLOGICAL EXPLANATION

Urushiol allergy is categorized as a delayed hypersensitivity type response on the basis of the time course of the reaction.[21] Many earlier studies reported that CD4+ cells would be effectors in contact dermatitis for delayed type hypersensitivity reactions,[30,31] but the results of Gocinski *et al*.[32] and Bour *et al*.[33] showed that CD8+ cells are the major effectors in *in vivo* experiments. In a study of the processing of urushiol haptens by both endogenous and exogenous pathways for presentation to T cells *in vitro*, the processing of urushiol for presentation to CD8+ T cells was inhibited by azide, monensin, and brefeldin A, suggesting that urushiol is processed by the endogenous pathway. On the other hand, presentation of urushiol to CD4+ T cells was inhibited by monensin but not by brefeldin A, suggesting compatibility with antigen processing by the endosomal pathway.[34] CD8+ cells can differentiate into effector cells in the absence of CD4+.[35] Lopez *et al*. reported that CD8+ T cells are the effectors of the contact dermatitis induced by urushiol, while CD4+ plays an important regulatory role in the onset of the response.[36] A recent study on cross-reactions between mango contact allergens and urushiol points out that the allergenicity of urushiol depends on the number of side chain double bonds in the third position in catechols; that is to say, diolefin is more allergenic than monoolefin in urushiol.[37] Xia *et al*. believed that lipoxygenase plays an important role in the contact dermatitis induced by urushiol.[38] Although many immunology[39-41] and clinical[42-44] studies have attempted to reveal the mecha-

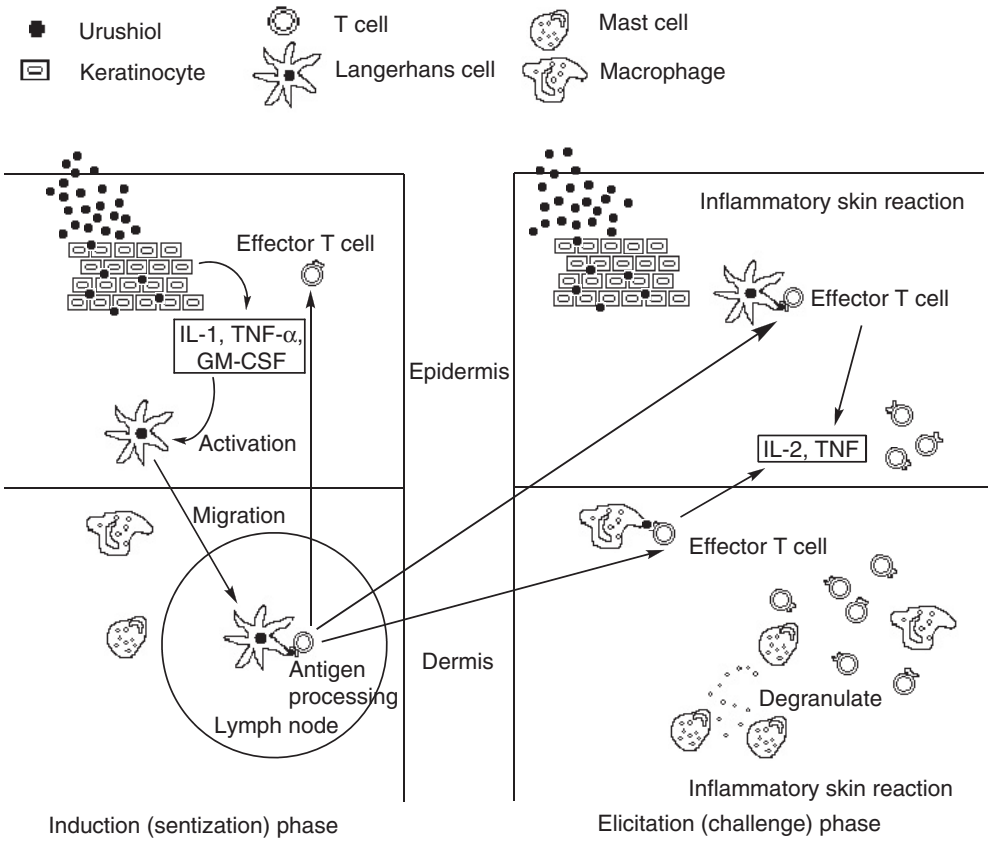


Fig. 2 Induction of sensitization of urushiol allergy.

nism of contact dermatitis induced by urushiol, no clear conclusion has been accepted yet.

ALLERGIC MEDICATION

There are many reports on the treatment of poison ivy and poison oak allergies.[45-48] Because the allergens of poison ivy/oak have the same structure as urushiol, the treatment methods and medicines also can be used to treat dermatitis caused by urushiol. Guin pointed out that barrier creams, protective clothing, and especially disposable vinyl gloves are useful in reducing exposure.[49] This method is effective not only for persons with outdoor occupations such as forest firefighters but also for lacquer workers. Chinese, Japanese, and Korea lacquers contain urushiol, while Vietnamese and China Taiwan area lacquers contain laccol, and Myanmar, Thai, and Laotian lacquers thitsiol. In 1590, in the Ming Dynasty of China, Li Shizhen found that China fir soup, purple perilla soup, sealwort soup, and crab soup were useful for treatment of contact dermatitis induced by lacquer sap.[50] Santucci *et al*. found that after 0.01% aqueous α-methylen-χ-butyrolactone was used to treat a contact dermatitis induced by *Alstroemeria ligtu*, a significant improvement in clinical manifestations was observed.[51] Forest workers in Thailand have discovered an effective medicine made from an extract of boiled teak leaf.[52] Baldwin *et al*. showed that contact sensitivity in response to urushiol was downregulated following treatment with a monoclonal antibody reacting with the allergen urushiol, of course, this phenomenon only is observed in mice until now.[53] Yarbrough *et al*. developed a medicine using ethoxylate in combination with sodium lauryl sarcosininate, and believed that this combination binds to the available urushiol receptors, rendering them inactive.[54] Although antihistamines, benzocaine derivatives, and corticosteroids have a weak inhibitory effect on itch in some dermatitis cases, when applied to the skin, they can cause superimposed forms of contact dermatitis in many people, and can not be recommended by the dermatologists. Thus, if the rash worsens after treatment, the affected person should suspect that an allergic reaction to the treatment and see a physician in a timely fashion.

PREVENTION

There is an English adage "Leaves of three, let them be." That is to say, avoidance of poison ivy, oak, and sumac is obviously the best method for preventing allergic contact dermatitis. Learning to identify members of the *Toxicodendron* genus is a must. However, for the lacquerware workers, direct contact with lacquer sap is inevitable, and can become a serious oc-

cupational skin disease. Establishment of spontaneous hyposensitization has been researched by Kligman[24] and Kawai.[17] In Korea, according to their traditional folk medicine, Koreans believed ingestion of lacquer to be effective for the treatment of gastrointestinal disease or simply be good for health in general, but Park *et al*. showed that ingestion of lacquer can cause severe systemic or cutaneous reaction accompanied by acute itching, even in those not previously known to be allergic to it.[55] For a sensitized person, avoiding direct contact with unhardened resin in furniture and fumes during the process of resin purification, and staying away from lacquer tree and sap are recommended. It is necessary for a lacquerware worker to wash the exposed areas as soon as possible after exposure to lacquer sap. Most urushiol can be removed with soap and water within 15 minutes, but after that period the urushiol is chemically bonded to the skin. Urushiol may be transferred to the skin from clothing or tools, so it is important to wash clothing and other materials with soap and water after exposure to urushiol. Because urushiol is oily and not very water soluble, pretreating clothes with alcohol may help remove the urushiol. There is an inexpensive commercial product, Tecnu poison oak-poison ivy cleanser that is somewhat better than alcohol at removing urushiol. It has reportedly been found effective when used even up to 48 hours after exposure.[56]

CONCLUSIONS

Rhus dermatitis caused by lacquer has the characteristics of delayed type hypersensitivity and is known to be the result of sensitization to the structure of a catechol derivative, urushiol. Contact hypersensitivity to urushiol is widespread, resulting in various degrees of reaction. Although there are many studies of contact dermatitis due to urushiol in immunology and cell biology, the allergic mechanism is not yet thoroughly clear. "Leaves of three, let them be" is an old adage to help people remember which plants they should avoid, but this advice is not completely accurate. While poison oak and poison ivy leaves usually come in threes, some plants may have five or seven leaves, and lacquer trees have seven to thirteen leaves. There is currently nothing special drug for the contact dermatitis caused by urushiol that provides immediate relief. Avoidance of lacquer trees and lacquer sap is recommended. Workers whose occupations involve lacquer must wear clothing with long sleeves, long pants, and gloves, and wash with soap and water immediately after exposure to urushiol.

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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