



Contents lists available at ScienceDirect

Allergy International

journal homepage: <http://www.elsevier.com/locate/alit>

Letter to the Editor

Anaphylaxis to ginger induced by herbal medicine

Dear Editor,

Ginger is considered to be good for health and widely used as a spice or antidote. While beneficial effects of ginger for prevention and amelioration of allergic diseases have been reported,^{1,2} ginger allergy is very rare despite its wide usage. A case with ginger-specific immunoglobulin E (IgE) sensitized by the industrial dust from spices was reported back in 1985.³ In 2002, however, a skin prick test (SPT) with ginger was negatively observed in 589 cases of food allergy.⁴ Recently, some cases with IgE-mediated ginger allergy have been reported and cysteine proteinase GP-I has been detected as a candidate allergen.^{5–7} Meanwhile, use of herbal medicine is expanding because it is easy to obtain as an over-the-counter drug and considered positively because it is “natural” and mostly harmless. However, frequent application of natural product would rather increase the risk of allergy for any food containing the same product. We report a case of anaphylaxis to ginger induced by taking herbal medicine.

A 59-year-old Japanese woman was introduced to our outpatient clinic for close examination of the cause of her anaphylaxis. She has history of rheumatoid arthritis, hypertension, cedar pollen allergy, and skin eruptions induced by infliximab, pyrazolone drugs, iodine, lidocaine, vitamin preparations, and dairy products. Additionally, she has felt sick after taking cold remedies or raw eggs.

In 2013, she took a dose of herbal medicine, Keimei Gashinsan (KG; Keimeido), for motion sickness in a plane flying to Korea. Although she had taken this medication several times without any trouble more than twenty years previously, this time she felt pruritus throughout her whole body soon after taking it. On arriving in Korea, she lost consciousness and was taken into the emergency room of a university hospital. She was diagnosed with anaphylactic shock and put on an artificial ventilator breathing system. After accompanying lung embolism and digestive bleeding were recovered, she returned safely to Japan.

The following year, she again developed dyspnea and itchy rash on her whole body, after taking another herbal medicine, Daiichi Sankyo Ichoyaku (DSI; Daiichi Sankyo Healthcare), for digestive complaints. She was initially seen by a local doctor following her rheumatoid arthritis, and was hospitalized due to hypoxemia. She recovered after an infusion of corticosteroid for treatment of anaphylaxis. DSI had been taken several times over the previous seventeen months.

As described in its accompanying leaflet, KG has been reported to cause anaphylaxis, for which the main ingredient, zedoary, is

responsible. DSI, however, does not contain zedoary. The only component common to these two medicines is ginger. To determine the components responsible for anaphylaxis in our case, a SPT was performed for all five components of KG including powdered zedoary, powdered ginger, powdered turmeric, powdered Japanese kelp and microcrystalline cellulose, and fourteen components of DSI including taka-diastase N1, lipase AP12, bacillus coagulans, species of lactic acid-forming bacillus bacteria (butyric acid), Japanese mallotus essences, powdered glycyrrhiza, magnesium aluminosilicate, hydrotalcite, magnesium hydroxide, powdered phellodendron bark, powdered cinnamon bark, powdered fennel, powdered clove and powdered ginger, as well as the whole preparations of KG and DSI. Although 20% aqueous solutions were prepared, most of them were insoluble and the supernatant of saturated aqueous solutions were used. Saline and 1% histamine were used for a negative and a positive control, respectively. Fifteen minutes after each of the sequential pricks, only zedoary, turmeric and ginger contained in KG and ginger in DSI induced itchy rashes with central wheals (Fig. 1a). As diameters of the wheals were all longer than a half of that induced by 1% histamine, they were all determined as positive (4+ to 2+). Notably, itchy pale red flare with scattered dark red spots covered both of her palms soon after finishing all pricks and lasted for around half an hour (Fig. 1b). She had noticed similar itchy palm rash after drinking ginger ale, eating curry or ginger pork, but it was unclear when it had onset and why it had never developed anaphylaxis. No other apparent delayed responses were observed. From these findings, our patient was diagnosed with the immediate-type allergy to zedoary/turmeric/ginger-containing drugs and foods, and recommended to avoid them. After that, she has never experienced anaphylaxis.

It should be noted that zedoary, turmeric and ginger are all derived from rhizomes of perennials belonging to the Zingiberaceae family (summarized in Table 1). This family contains the genera *Zingiber*, *Curcuma* and *Kaempferia*, and *Curcuma* further contains *C. longa* (turmeric), *C. aromatica* (wild turmeric), and *C. zedoaria* (zedoary). Curcumin is the main component of turmeric, whereas zedoary contains no curcumin. In contrast, one case showing anaphylaxis by KG and positive reaction to both zedoary and turmeric by a scratch test has been reported in a meeting abstract (Yagi Y *et al.*, 2004). Very recently, a case of anaphylaxis by black ginger (*Kaempferia parviflora*) was reported and the reaction was possibly to a common allergen among *C. zedoaria*, *C. longa*, *C. aromatica* and *Z. officinale* (ginger), as well as *K. parviflora*.⁸ These results support an idea that there are common antigenic components among zedoary and turmeric, and more widely, and ginger.

The current case safely took ginger-containing DSI several times soon after development of anaphylaxis to KG. This suggests that she

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2019.08.009>1323–8930/Copyright © 2019, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

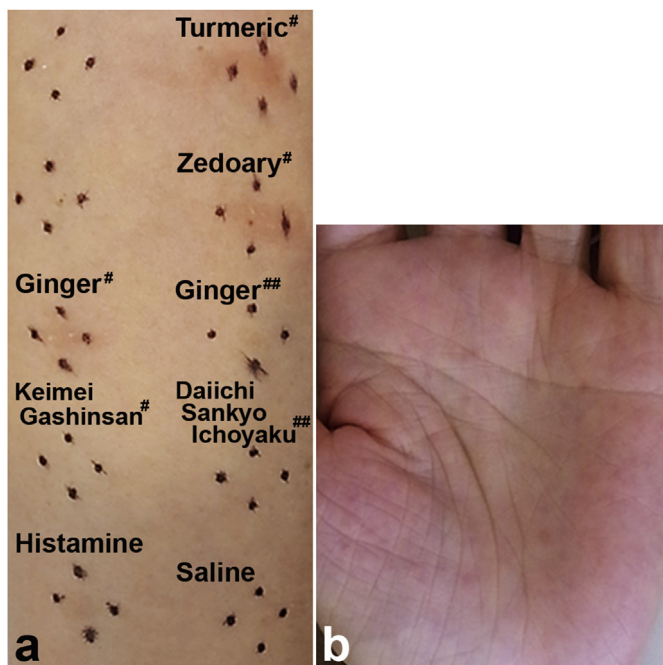


Fig. 1. Skin prick test with components of herbal medicines. **(a)** Positive reaction was observed to saturated aqueous solutions of turmeric (15 mm: 4+), zedoary (15 mm: 4+) and ginger (7 mm: 3+) in Keimei Gashinsan(*) and ginger (4 mm: 2+) in Daiichi Sankyo Ichoyaku(##) by the skin prick test. Saline and 1% histamine (5 mm) were used as a negative and a positive control, respectively. The diameters of developed wheals and their positivities were indicated in parentheses. **(b)** Palm rash was observed soon after the end of the skin prick test.

Table 1
The Zingiberaceae family plants.

Family	Genus	Species	English name	Japanese name
Zingiberaceae	Zingiber	<i>Z. officinale</i>	ginger	shōkyō (shōga)
		<i>Z. mioga</i>	Japanese ginger	myōga
	Curcuma	<i>Z. zerumbet</i>		hanashōga
		<i>C. longa</i> (<i>C. domestica</i>)	turmeric	ukon (akiukon)
		<i>C. aromatica</i>	wild turmeric	kyō-ō (haruukon)
		<i>C. zedoaria</i>	zedoary	gajutsu (murasakiukon)
		<i>C. xanthorrhiza</i>	Javanese turmeric	jawaukon
	Kaempferia	<i>K. parviflora</i>	black ginger	kuroshōga
		<i>K. galanga</i>	galangale	ban-ukon

had not been sensitized by ginger at the first anaphylaxis, but developed ginger allergy during taking DSI through cross-reactivity to zedoary and turmeric uniquely contained in KG. Although we assumed the common antigenicity among zedoary, turmeric and ginger as suggested in Reference 8, we have failed

to identify their common antigenic component with western blotting (data not shown). Furthermore, although spice allergy can reportedly be induced by a cross-reactivity of some particular pollen-specific IgE, such as mugwort and birch,⁹ a cross-reactivity between spices and cedar pollen, to which the patient was allergic, has never been reported. Therefore, the mechanism of developing ginger allergy in the current case is still unclear and remains to be further investigated.

Although rare, the possibility that ginger allergy can be induced by taking herbal medicine should be considered.

Acknowledgement

We acknowledge critical reading by Patricia Gehlhaar in Allergy Department Hospital Universitario Ramón y Cajal and proofreading by Benjamin Phillis in Clinical Study Support Center of Wakayama Medical University. There is no funding support on this report.

Conflict of interest

The authors have no conflict of interest to declare.

Hisako Okuhira, Yumi Nakatani, Fukumi Furukawa,
Nobuo Kanazawa *

Department of Dermatology, Wakayama Medical University, Wakayama, Japan

* Corresponding author. Department of Dermatology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-0012, Japan.
E-mail address: nkanazaw@wakayama-med.ac.jp (N. Kanazawa).

References

1. Park G, Oh DS, Lee MG, Lee CE, Kim YU. 6-Shogaol, an active compound of ginger, alleviates allergic dermatitis-like skin lesions via cytokine inhibition by activating the Nrf 2 pathway. *Toxicol Appl Pharmacol* 2016;**310**:51–9.
2. Kawamoto Y, Ueno Y, Nakahashi E, Obayashi M, Sugihara K, Qiao S, et al. Prevention of allergic rhinitis by ginger and the molecular basis of immunosuppression by 6-gingerol through T cell inactivation. *J Nutr Biochem* 2016;**27**:112–22.
3. van Toorenbergen AW, Dieges PH. Immunoglobulin E antibodies against coriander and other spices. *J Allergy Clin Immunol* 1985;**76**:477–81.
4. Moneret-Vautrin DA, Morisset M, Lemerdy P, Croizier A, Kanny G. Food allergy and IgE sensitization caused by spices: CIBAA data (based on 589 cases of food allergy). *Allerg Immunol (Paris)* 2002;**34**:135–40.
5. Gehlhaar P, González-de-Olano D, Madrigal-Burgaleta R, Bartolomé B, Pastor-Vargas C. Allergy to ginger with cysteine proteinase GP-I as the relevant allergen. *Ann Allergy Asthma Immunol* 2018;**121**:624–5.
6. Schmidt J, Dahl S, Sherson DL. Allergic rhinoconjunctivitis caused by occupational exposure to ginger. *Ugeskr Laeger* 2015;177 (in Danish).
7. Sato H, Manki S, Manki A, Ishii T, Watanabe H. A case of food-dependent exercise-induced anaphylaxis induced by ginger. *Pediatrics Japan* 2018;**59**:453–6 (in Japanese).
8. Hayashi E, Sowa-Osako J, Fukai K, Natsumi A, Yagami A, Sato N, et al. Case of anaphylaxis caused by black ginger in a dietary supplement. *J Dermatol* 2019;**46**:e56–7.
9. Chen JL, Bahna SL. Spice allergy. *Ann Allergy Asthma Immunol* 2011;**107**:191–9.

Received 30 April 2019

Received in revised form 12 August 2019

Accepted 23 August 2019

Available online xxx