

Common food flavors are safe in patients with urticaria or atopic dermatitis

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Clinical Implications

- Seventy-nine patients with chronic spontaneous urticaria or atopic dermatitis were exposed orally to common food flavors. The challenges did not aggravate either condition, suggesting that food flavors are largely irrelevant as triggers of both diseases.

TO THE EDITOR:

Low molecular weight preservatives, flavors, colors, antioxidants, taste enhancers, and sweeteners are widely used to improve quality, appearance, customer perception, and durability of food products.¹ The evidence for allergic and pseudoallergic reactions following ingestion of such additives has been reviewed recently.² Data on the frequency of pseudoallergic reactions to food additives are scarce and have been reported with a broad variability of results.³⁻⁵ In addition, considerable time has elapsed since publication of most reports.² The paucity of evidence-based data creates room for self-perceived causal relations, myths, fake facts, and charlatanry related to putative harmful side effects of food additives.

Food flavors comprise natural compounds (eg, from plants), nature-identical substances (artificially produced but identical to naturally occurring food components), and artificial flavors (artificially produced, not found in natural food).⁶ All these have been described anecdotically or in small case series as potential triggers of chronic spontaneous urticaria (CSU)⁷ or atopic dermatitis (AD),⁴ albeit without proven evidence. This less-than-optimal situation prompted us to evaluate the occurrence of allergic or pseudoallergic reactions to 18 of the most frequently used food flavors in patients with preexisting CSU or AD.

Two hundred eighteen adults with preexisting AD ($n = 74$), CSU with or without angioedema ($n = 103$), or allergic rhinitis with pollen-related food allergy ($n = 41$) were recruited into study phase I (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org). All patients suspected food allergy as the relevant trigger for their complaints. The study was conducted in accordance with the institutional, state, and federal guidelines and was approved by the local ethics committee.

We selected 18 food flavors most commonly used in Europe ([Table I](#)). All these compounds had been approved by the Flavor and Extract Manufacturers Association of the United States and are listed in their “generally recognized as safe” category. In the first phase of the study, skin prick tests (SPTs) were performed in all patients according to the European Academy of Allergy and Clinical Immunology recommendations to identify IgE-mediated

allergies. Suitable SPT concentrations of each substance were determined beforehand by testing healthy volunteers with test concentrations 0.1%, 1.0%, 10%, and 100%. All compounds were diluted in ethanol 70% in water, except for myrcene, which was used in benzyl alcohol 4% in water. The highest concentration that did not provoke irritant skin reactions in healthy volunteers was selected (10% for all flavors, except for benzaldehyde, which was used at a concentration of 0.1%). SPT in all 218 patients with all 18 flavors revealed no relevant skin reaction to any of the substances tested, nor did any unwanted side effect occur.

In the second phase, 79 randomly selected patients with AD or CSU from the first phase were challenged orally (29 patients with AD and 50 patients with CSU; [Table II](#)). No oral challenges were performed on the allergic rhinitis with pollen-related food allergy group. Dosages were chosen according to average daily intakes of the respective flavors, multiplied by a safety factor of 5 to account for any unbalanced diets (challenge doses and protocol are depicted in [Table I](#)). Before oral challenges, patients had no or only mild symptoms of their disease (no significant wheals in CSU for 4 days, SCORing Atopic Dermatitis score <20 in AD). Furthermore, antihistamines were prohibited 4 days before testing, and phototherapy, topical or systemic corticosteroids, and other immunosuppressants were suspended for at least 2 weeks. In addition, the patients followed a low-pseudoallergen diet including no flavors according to published guidelines⁸ for 4 days before testing, and they remained on this diet during oral challenges. Defined *en-bloc* mixtures of food flavors were administered orally unblinded over 4 consecutive days ([Table I](#)). For safety reasons, patients were hospitalized during these days.

In case of a positive reaction, which was defined as an exacerbation of AD, or occurrence of angioedema or urticaria in CSU within 24 hours of intake of the daily flavor mixtures, patients were exposed unblinded to the individual substances contained within the respective mixture in 2-hour intervals. In case of positive reactions to the individual substances, double-blinded placebo-controlled food challenges (DBPCFCs) were intended. However, because few patients reacted and the single individual who qualified for DBPCFC refused to participate, no DBPCFCs were performed.

In oral challenge tests, no patient with AD showed skin flares after challenge ($n = 29$). In patients with CSU ($n = 50$), we observed positive reactions in 6 patients during oral challenge with *en-bloc* mixtures ([Table II](#)). Four of these 6 patients were re-tested with single preparations of the critical flavor mixtures, without any reactions. One patient withdrew consent to re-test with the individual flavors of the mixture. The last patient displayed a positive reaction to ethyl butyrate but, unfortunately, refused DBPCFC with ethyl butyrate. However, because patients with CSU were off antihistamines 4 days before oral challenge tests, and challenge tests with the mixtures lasted for 4 additional days, some spontaneous disease activity in patients with CSU could be reasonably expected.

Determining appropriate challenge doses is notoriously difficult, and we have chosen doses of food flavors that patients may encounter in their daily diet. In principle, higher doses might have elicited different results. Likewise, hypersensitivity reactions

TABLE I. Food flavors* tested in this study

Day of oral food challenge	S. no.	Flavor	Oral dose for food challenge (mg)
Day 1	1	Trans-Anethole	100
	2	Cis-3-Hexenol	15
	3	α -Terpineol	10
	4	Ethyl butyrate	60
	5	Iso-Amyl Butyrate	30
Day 2	6	Benzaldehyde	100
	7	δ -Decalactone	20
	8	δ -Dodecalactone	5
	9	Caprylic acid	10
Day 3	10	Acetoin	20
	11	Myrcene	10
	12	Hexyl acetate	20
	13	Menthol	90
	14	Vanillin	200
Day 4	15	Furaneol	10
	16	Raspberry ketone	50
	17	Ethyl vanillin	15
	18	Methyl cinnamate	5

OFC, Oral food challenge.

*Most commonly used food flavors in Europe. In the first phase, 218 patients (details in Table E1) underwent SPTs with these substances. In the second phase, 79 hospitalized study patients (randomly selected patients with AD or CSU from the first phase) were challenged orally with *en-bloc* mixtures of 3-5 flavors on 4 consecutive days as indicated.

TABLE II. Results of oral challenges to food flavors

Patients tested	AD	CSU	CSU + AE	Total
All patients	29	23	27	79
Patients with positive OFC to mixture	0	1	5	6
Patients with positive OFC to single substances	—	0	1	1

AE, Angioedema; OFC, oral food/food challenge.

No patient with AD developed skin flares. Initially, 6 patients with CSU showed positive reactions to *en-bloc* flavor challenges. Only 1 patient displayed a second positive reaction during OFC.

in individual patients cannot be completely excluded and should be considered, if the patient's history is compelling. Our study demonstrates the extensive clinical protocol necessary to elucidate the potential roles of food flavors in AD and CSU. It needs to be emphasized that any diagnostic diet needs to be monitored by a trained dietician. The efficacy of diets has to be evaluated thoroughly to avoid unnecessary or unbalanced diets.

In summary, some food additives have been previously implicated to trigger disease activity in patients with AD^{4,9} or CSU.⁷ Our study now comprehensively substantiates that allergic or

pseudoallergic reactions to food flavors in these conditions are very rare. Only ethyl butyrate, an ester with fruity-juicy scent and taste reminiscent of pineapple,¹⁰ was suspected to trigger CSU in 1 out of 79 patients, although spontaneous activity is not unlikely in this case. We therefore conclude that food flavors are largely irrelevant in patients with CSU and AD and that the underlying condition is likely to cause symptoms as opposed to the food flavor itself.

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TABLE E1. Patient population (n = 218) for SPTs and oral challenge with food flavorings

Category	Value
Age (y), mean $\pm$ SD	37.0 $\pm$ 15.6
Body weight (kg), mean $\pm$ SD	76.9 $\pm$ 16.0
Sex, n (%)	
Male	81 (37.2)
Female	137 (62.8)
Preexisting conditions, n (%)	
AD	74 (33.9)
CSU $\pm$ AE	103 (47.3)
AR + FA	41 (18.8)

AE, Angioedema; AR, allergic rhinitis; FA, food allergy.