

Allergic conjunctivitis to chamomile tea

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Eye washing with chamomile tea is a folk remedy used by the general public to treat conjunctivitis and other ocular reactions. Chamomile is also found in many cosmetic products. Some cases of contact dermatitis (but not reactions of type I) were reported following its topical applications. We present seven hay fever patients that suffered from conjunctivitis; two of them also had lid angioedema after eye washing with chamomile tea. All seven patients had positive skin prick tests to the chamomile tea extract, Matricaria chamomilla pollen and Artemisia vulgaris pollen extracts. Positive conjunctival provocations were also observed in all the patients with the chamomile tea extract. In contrast, no symptoms were observed after oral challenges with this infusion. IgE activity against chamomile tea and Matricaria and Artemisia extracts (composite pollens) was detected by ELISA in the seven patients' sera. A cross reactivity among the above extracts was observed by an ELISA inhibition study. In all cases, the IgE activity to chamomile tea could fully be absorbed by Matricaria pollen extract.

Skin prick tests and conjunctival provocation tests also performed in 100 hay fever controls revealed a positive immediate skin response to Artemisia in 15 patients, eight of them also to Matricaria pollen and five of them to Chamomile tea as well. Only two of the last patients had a positive conjunctival response. The results were negative in the rest of the controls.

We conclude that the chamomile tea eye washing can induce allergic conjunctivitis. Matricaria chamomilla pollens contained in these infusions are the allergens responsible for these reactions.

INTRODUCTION

The term 'chamomiles' is used to mean a large group of species belonging to the Compositae family.¹ The most important of them is probably *Matricaria chamomilla*, given that the solution made from its dried flower heads (chamomile tea) has been available commercially and is now a common drink worldwide.² Its wide distribution is partly due to the multiple phytotherapeutic properties attributed to it. Chamomile is used as a familiar remedy for treating insomnia, indigestion, and menstrual disorders, as well as other afflictions^{2,3} and recently has been used successfully in treating migraine.⁴ It also has a mild antiphlogistic and bacteriostatic activity for which it is also used as a

topical phytotherapeutic agent. It is used in treating epidermolysis bullosa,⁵ eczema, eye irritation, throat discomfort, and hemorrhoids.³ Chamomile is also found in many cosmetic products (shampoo, hair rinses, and as a vegetable hair dye).⁶ Nevertheless, chamomile has also been shown capable of causing allergic reactions. Cases of anaphylaxis have been described following its ingestion.⁷⁻⁹ A type I immunologic mechanism has been implicated in these reactions,^{7,9} and IgE activity against *Matricaria chamomilla* pollens found in these infusions has been reported.⁹ Also, allergic contact dermatitis has occurred in subjects who have handled this plant, or who have used compresses of chamomile or chamomile ointment.^{6,10-15}

The purpose of this article is to present seven patients who suffered conjunctivitis following chamomile tea eye washings. The results of the investigation carried out suggest that these reactions were produced by a type I IgE-mediated immunologic mechanism.

MATERIAL AND METHODS

Subject

Seven patients who had suffered conjunctivitis following eye washing with chamomile tea were studied (Table 1). The patients decided to try rinsing their eyes with chamomile tea in the hopes of finding relief from styes or runny eyes. Instead, all of the patients suffered severe conjunctivitis following the eye washing. The conjunctival reactions were immediate and two of them were associated with lid angioedema. In one of the last patients, treatment with epinephrine at an emergency unit was necessary.

As shown in Table 1, all of them had histories of seasonal rhinitis or asthma. In patient 4, ingestion of honey caused swelling of the lips. Some days later he put a little of this honey on his tongue, and it caused his mouth to itch. Patient 7 developed a "scratchy" feeling in his throat after ingestion of sunflower seeds.

As control and to determine the prevalence of allergic conjunctivitis

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Table 1. Clinical Characteristics of Patients

Patient	Age, yr	Sex	Atopic History	Conjunctivitis to Chamomile Tea	Other Allergic Reactions
1	37	M	Seasonal asthma May → June	Yes	None
2	29	F	Seasonal rhinitis May → June	Yes	None
3	51	F	Seasonal rhinitis May → June	Yes*	None
4	21	M	Seasonal rhinitis May → June	Yes	Pruritus and angioedema after ingestion of honey
5	48	F	Seasonal rhinitis May → June	Yes*	None
6	49	M	Seasonal rhinitis May → Sept	Yes	None
7	39	M	Seasonal asthma May → June	Yes	Itching in the throat following ingestion of sunflower seeds

* Conjunctivitis and lid angioedema.

to chamomile tea, we also performed *in vivo* studies (skin and conjunctival provocation tests) in 100 consecutive hay fever patients.

Antihistamines were discontinued in all patients at least 1 week before and during the test period.

Preparation of Allergen Extracts

Two grams of commercial chamomile tea dust was defatted with acetone and extracted in 20 mL of 0.01 M phosphate, 0.15 M NaCl, pH 7.4 (PBS). The mixture was stirred for 24 hr at 4 °C, then paper filtered (Whatman, Maidstone, England) and centrifuged (5000 g; 20 minutes). The supernatant was recovered and sterilized by 0.22 µm filtration (Millipore, Molsheim, France). The final concentration was 1:10 wt/vol. Protein concentration was determined by using Bio-Rad protein assay (Bio-Rad, Richmond, USA).

The same procedure was used to extract the antigens from the following pure pollen samples: *Matricaria chamomilla* (Allergon A. B. Engelholm, Sweden) and *Artemisia vulgaris* (Miles Martin, Spokane, USA).

Skin Tests

All of the above mentioned extracts and a battery of commercially available common allergens that included *D. pteronyssinus*, *Phleum pratense* (Timothy), *Olea europaea* (Olive), molds, and danders (Dome-Hollister-Stier, Spokane, USA) were

used for skin prick testing. Histamine dihydrochloride (1 mg/mL) was used as a positive control, and 50% glycerol was used as a negative control. All skin test sites were read after 15 minutes, and a wheal of at least 3 by 3 mm was considered positive.

End-point titration tests were performed with 10-fold dilutions of chamomile tea extract. The minimal concentration that produced a wheal of 1 to 2 mm with flare and itching in the prick test was considered the end-point dilution.

Conjunctival Provocation Test

Conjunctival provocation tests (CPT) were performed following the technique previously described.¹⁶ At that time the conjunctival examination performed on all patients was normal. At least 6 weeks had passed since the disappearance of their previous conjunctival reaction. The test was performed outside the pollen season. We began administering one drop of the 1:1,000,000 wt/vol concentration of chamomile tea extract in the conjunctival sac. If no reaction was noted within 20 minutes, the next concentrations, progressively increased by tenfold, were applied in the conjunctival sac of the other eye. One drop of PBS diluent was applied in the opposite eye as a negative control. The criterion for positive CPT was congestion of the conjunctival mucosa and itching of the eye.

Oral Challenge with Chamomile Tea

Placebo double-blind oral provocations were performed in seven patients. They were instructed to stop antihistamines, oral cromoglycate, and ketotifen 1 week before the chamomile tea challenges. β_2 -Agonists, theophylline, and inhaled cromoglycate were stopped 12 hours before the procedure. No patient had received systemic steroids within 1 month before admission to the study. Different dilutions of chamomile tea were ingested by the patients. Orange juice was used as placebo. The chamomile tea dilutions were mixed with the orange juice to mask the taste and color. A member of the staff randomized all challenges so the investigators and patients were unaware of the content of any challenge. We began with 50 mL of 1:10,000,000 wt/vol chamomile tea. The patients were also followed clinically by a physician who noticed the eventual symptoms of urticaria, angioedema, nausea, vomiting, diarrhea, abdominal pain, pruritus or asthma. Also FVC and FEV₁ were measured on a Vitalograph-PFT spirometer (Buckingham, UK), before the challenges and every 30 minutes thereafter. If no symptoms or a 20% decrease in FEV₁ were observed in the following two hours, another 50 mL of the next concentration was given. They were progressively increased by tenfold until reaching 1:100 wt/vol maximal concentration. Only two different dilutions were administered each day.

Enzyme-Linked Immunosorbent Assay (ELISA)

This was performed as previously described.⁹ Briefly, the wells of a polystyrene 96-well microplate (Nunk, Roskilde, Denmark) were coated with chamomile, *Matricaria*, or *Artemisia* extracts at a protein concentration of 5 µg/mL in PBS. After an overnight incubation at 4 °C, the plates were washed (PBS 0.1% tween 20) and neutralized with 1% of bovine serum albumin

(BSA; Sigma, St. Louis, USA) in PBS (PBS-BSA) for one hour at room temperature. After washing, 100 μ L of undiluted serum were added per well, and the plates incubated four hours at room temperature. Then the wells were washed and filled with 100 μ L of 1:4000 dilution (PBS-BSA) of affinity-isolated goat F(ab')₂ antibodies to human ϵ chain fragments, conjugated with peroxidase (Tago Inc, Burlingame, USA). These labeled antibodies were chosen for their lack of cross-reactivity with human IgG in the assay conditions used. After an overnight incubation at 4 °C and a final washing step, 100 μ L of substrate solution (0.05% H₂O₂, 0.02 M *o*-phenylenediamine, 0.1 M citrate buffer, pH 5.5) were added. The enzymatic reaction was stopped with 100 μ L of 2N HCl and the

absorbance values were measured at 492 nm (SLT 210; Kontron, Grödig, Austria).

Inhibition Assays

Cross-allergy studies were performed as described by Gleich et al¹⁷ but using ELISA. Briefly, 100 μ L of a 1:2 dilution in PBS of the patients sera was mixed with the same volume of a number of serial dilutions of each extract sample, previously adjusted to 250 μ g/mL in protein. In every inhibition assay the same amount of an unrelated antigen (*D. pteronyssinus* extract, α base Dome-Hollister-Stier Bridgend, UK), was included. After overnight incubation at 4 °C, all samples were tested for specific IgE as above without further dilution.

For specificity control, ten sera containing IgE to *D. pteronyssinus*

were incubated under the same conditions with the above extracts or PBS. In these cases, ELISA was performed with *D. pteronyssinus*-coated wells (3M Diagnostic Systems, Inc, Santa Clara, CA) following the same procedure described before.

RESULTS

Skin, Conjunctival and Oral Provocation Tests

All the patients showed an immediate positive skin response to chamomile tea extract, as well as to *Matricaria chamomilla*, *Artemisia vulgaris*, and grass pollen extracts. Likewise, prick tests were positive with heated chamomile tea (ten minutes at 90 °C) in the seven patients (Fig 1).

The conjunctival provocation tests were also positive in all of them with low concentrations of the chamomile tea extract (Fig 2). In most patients there was an association between the end-point dilution (skin tests) and the positive dilution in the conjunctival provocation test (Table 2).

All control subjects showed positive skin tests to grass and fifty to *Olea pollen* extract. Fifteen had positive prick tests to *Artemisia*, eight of them to *Matricaria* pollen, and five of them in addition to chamomile tea. Only two of the last patients had a positive conjunctival response to chamomile tea extract 1:100 wt/vol.

The seven patients tolerated the ingestion of chamomile tea with no problem.

Specific IgE Measurement

The presence of circulating IgE antibodies to antigens contained in chamomile tea extract was studied by ELISA. As shown in Figure 3 all seven patients had detectable IgE activity to this extract, whereas this activity was not found in the 28 healthy individuals used as controls. This activity was fully absorbed by a prior serum incubation with chamomile tea extract (not shown), but not with the same amount of an



Figure 1. Prick test result with unheated (F) and heated (C <90 °C, ten minutes) chamomile tea extract dilutions.



Figure 2. Positive conjunctival provocation test with 1:100 wt/vol chamomile tea extract.

Table 2. Chamomile Data

Patient	Skin Prick Tests*		End-Point Titration with Chamomile Tea† wt/vol	Positive Conjunctival Provocation Test with Chamomile Tea (wt/vol)
	Matricaria Pollen 1:10 wt/vol	Chamomile Tea 1:10 wt/vol		
1	12	12	1:1,000,000	1:100,000
2	7	6	1:100,000	1:100
3	20	11	1:10,000,000	1:1,000,000
4	9	8	1:100,000	1:100
5	13	11	1:100,000	1:1000
6	8	9	1:100,000	1:1000
7	19	15	1:10,000,000	1:1000

* Wheal largest diameter (mm).

† Extract dilution enough to elicit a small wheal of 1 to 2 mm with flare and itching.

unrelated antigen (31 $\mu\text{g/mL}$; *D. pteronyssinus*) (Fig 3). In all cases such IgE activity was also removed when sera were first absorbed with *Matricaria* pollen extract (31 $\mu\text{g/mL}$) or, in most patients, with the same amount of *Artemisia* pollen extract (Fig 3). In two patients (patients 4 and 6), however, *Artemisia* pollen extract was unable to absorb most IgE activity to chamomile tea, even when higher amounts (>125 $\mu\text{g/mL}$) of this extract were used (not shown). These extracts (chamomile tea, *Matricaria*, and *Artemisia*) were completely unable to inhibit the IgE activity in a nonrelated ELISA system (*D. pteronyssinus*), indicating the specificity of the above inhibition studies.

RESULTS

The seven patients studied referred to having conjunctival inflammation a few minutes after the eye washings with chamomile tea. These reactions were reproduced in all of them by conjunctival provocation in our laboratory. In contrast, only two of the 100 control hay fever patients showed a positive conjunctival reaction to chamomile tea extract, ruling out that these were due to an irritating effect. Patients 1 and 3 had a positive conjunctival response to very diluted solutions of the extract (1:100,000 wt/vol and 1:1,000,000 wt/vol, respectively). This may explain the severe conjunctivitis that they referred to having suffered following

the eye washings with solutions of chamomile, (in one of them it was so intense that it required emergency service attention). These are usually prepared in a concentration of approximately 1 g (contained in the bag) in 100 to 200 mL of hot water (the capacity of a cup).

The underlying mechanism was probably an IgE-mediated immunologic reaction. These conclusions are supported by an immediate response in the prick tests and the presence of specific IgE to chamomile tea extract in all the patients. The negative results obtained in the control subjects support the specificity of these findings.

Heated chamomile tea extract (ten minutes at 90 °C) was still able to produce a positive skin response in all the patients. It therefore does not seem that the heat usually used in preparing these solutions greatly affects their allergenic activity.

The quality of chamomile tea depends on the concentration of the essential oil it contains. Since this active principle is maximum during the floration period, the plant is collected at this time.^{2,18} It is also at this time that the content of pollen inside the anthers is greatest.¹⁹ In fact, we were able to find by microscopic examination, large quantities of *Matricaria chamomilla* pollens in all commercially available chamomile teas tested so far.⁹ In this sense, the seven patients also showed a positive skin prick test to *Matricaria* pollen extract. Additionally, all the IgE activity detected *in vitro* against the chamomile tea extract was absorbed by the *Matricaria* pollen. These results would indicate that this component of the infusion was the allergen responsible for the reactions presented in our patients.

The question to be answered concerned the mechanism of sensitization to this pollen. The *Matricaria chamomilla* is an entomophilous plant²¹ and thus, sensitization by inhalation of this pollen is unlikely. The sensitization could have oc-

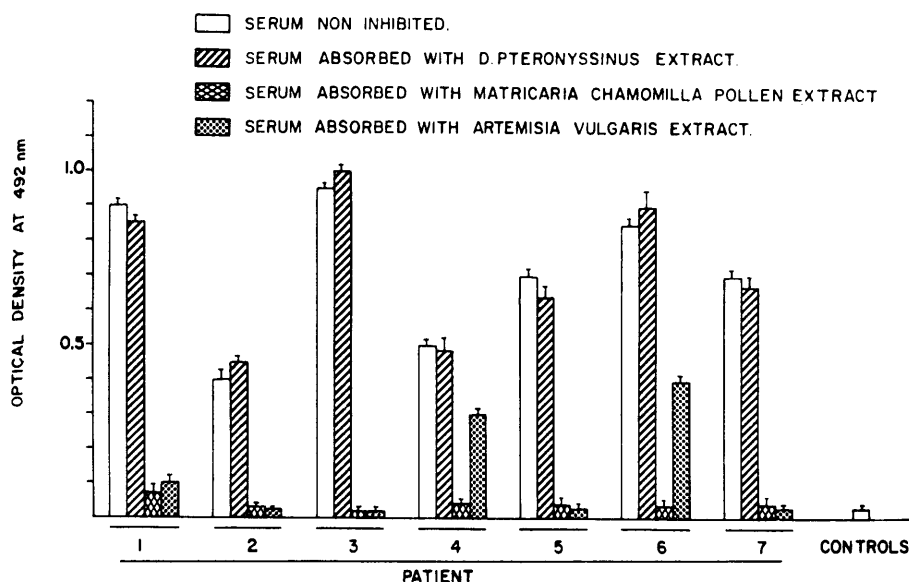


Figure 3. Specific IgE measurement (ELISA) to chamomile tea extract. Patients' sera were assayed without or with a prior absorption with 31 $\mu\text{g/mL}$ of the above extract as described in "Material and Methods" (mean $\pm$ SD of triplicates, except for controls that were 28 replicates).

curring from its ingestion (some of the patients remembered having drunk these solutions). Nevertheless all the patients sensitized to *Matricaria* pollen also showed skin response to *Artemisia*. Furthermore, a cross reactivity between *Matricaria* and *Artemisia* pollen could be observed in the ELISA inhibition studies, suggesting that indirect sensitization could also have been operational. This cross-reactivity is not surprising because *Matricaria* and *Artemisia* plants have a close taxonomic relationship. Both belong to the same *Compositae* family, and to the same tribe, *Anthemideae*.²⁰ *Artemisia* plants show an anemophilous pollination and are an important worldwide cause of hay fever.²⁰⁻²⁵ Likewise ragweed (composite pollen) is the most important cause of pollinosis in the United States,^{20,26} and cross-reactivity with the *Matricaria* has also been found.⁹ All of these facts might suggest that chamomile allergy could be a more common problem than is suspected.

The composite pollens may also produce allergic symptoms when ingested. Nausea, vomiting, diarrhea, hay fever, and asthma have been

described as not uncommon complications of oral immunotherapy with ragweed pollen.²⁷ Anaphylactic reactions have followed ingestion of *Helianthus annuus* and/or *Taraxacum officinale* (also composite pollens) present in some types of bee pollen and honey.²⁸⁻³² *Matricaria chamomilla* is not an exception, and has also been capable of producing anaphylaxis following its ingestion.⁷⁻⁹ In contrast, none of our patients had symptoms after drinking chamomile tea. This is not surprising because a large percentage of subjects with positive skin prick tests to foods tolerate their ingestion.^{33,34}

In conclusion, the results of the investigation carried out show that eye washings with chamomile tea can cause allergic conjunctivitis. The results also suggest that the allergens responsible are the *Matricaria chamomilla* pollens contained, probably as a consequence in most cases, of its cross reactivity with other sensitizing anemophilous composite pollens.

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FORMALDEHYDE AT RESIDENTIAL CONCENTRATIONS FAILS TO CAUSE AIRWAY OBSTRUCTION OR BRONCHIAL HYPERRESPONSIVENESS

In order to evaluate effects of formaldehyde on airway function and reactivity, the authors studied 15 nonsmoking adults with bronchial hyperresponsiveness to histamine. Participants had a mean PC₂₀ of 0.37 mg/mL and only one had a PC₂₀ greater than 1 mg/mL. Measurement of pulmonary function and responsiveness to histamine before and after exposure in a climate chamber for 90 minutes to clean air containing formaldehyde vapor, 0.008 mg/m³, 0.12 mg/m³, and 0.85 mg/m³ on different days disclosed no significant changes.

These data suggest residential levels of formaldehyde are not likely to contribute to pulmonary symptoms although interaction with other irritants or particulates might potentiate an adverse effect.

—RMS

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