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Original Article

Anti-allergic effect of apple polyphenol on patients with atopic dermatitis: A pilot study

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Abstract

The aim of the present study was to evaluate the anti-allergic effect of apple condensed tannins (ACT) in patients with atopic dermatitis (AD) as a pilot study. An ACT supplement given to the patients at oral doses of 10 mg/kg per day for 8 weeks reduced the inflammation, lichenification, cracking, itching, sleep disturbance and peripheral blood eosinophil counts. Itching and sleep disturbance scores after ACT supplement even for 2 weeks were significantly decreased compared with the control group. The results suggest that ACT has an anti-allergic effect and that its use improved the symptoms of AD.

Key words: anti-allergic effect, apple polyphenol, atopic dermatitis.

Introduction

Apples contain several phenolic substances: chlorogenic acid, catechin, epicatechin, phlorizin, rutin, flavonoid and condensed tannins.[1–7] Some of these substances have physiologic and pharmacologic activities. Osada *et al*. have demonstrated that apple condensed tannins (ACT), which are 10-fold higher in unripe apples than in ripe ones, scavenge active oxygen species.[8] Several authors have reported that oligometric catechins show antioxidant activities.[9,10] Recently, Kanda *et al*. have described that ACT has an inhibitory effect on histamine release from both rat basophilic leukemia (RBL-2H3) cells by antigen stimulation and rat peritoneal mast cells stimulated by compound 40/80.[11] These findings collectively indicate that ACT may have anti-allergic effects and therefore prompted us to evaluate their therapeutic effect on patients with atopic dermatitis (AD) in a pilot study.

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Methods

Sample preparations

The ACT from unripe apples were obtained according to the method reported by Ohnishi-Kameyama *et al*.[12]

Subjects

This pilot study was conducted at the Atopy Outpatient Clinic of Kojima Hospital, one of the affiliated institutions of Kansai Medical University. Twenty-four patients with AD, from whom informed consent was obtained, were enrolled in the study. They were alternatively divided into one of the two groups, the ACT group (14 patients) and the control group (10 patients, because four patients were dropped out). Their ages ranged from 8 to 18 years (Table 1). They had no other allergic diseases, including bronchial asthma and allergic rhinitis. The diagnosis of AD was made on the basis of the morphologic appearance and distribution of skin lesions, the clinical course and the family history of atopic disease, as described by Hanifin and Rajka.[13]

Study design

During the first 2 weeks of the study period (the observation period), the patients of the both groups were placed

Table 1 Characteristics of the patients with atopic dermatitis

	ACT group	Control group
No. subjects (male/female)	14 (6/8)	10 (4/6)
Age (years)	13.3 ± 3.8 (6–18)	14.1 ± 2.1 (11–17)
Serum IgE (IU/mL)	1944 ± 231 (137–8600)	2007 ± 1626 (290–6200)
Peripheral eosinophil counts (/μL)	760 ± 275 (280–1223)	784 ± 368 (290–1620)
Grading scores of AD	17.3 ± 3.0 (13–24)	16.4 ± 2.7 (13–22)
Duration of AD (years)	8.8 ± 3.9 (1–15)	6.1 ± 1.9 (3–10)

ACT, apple condensed tannins; AD, atopic dermatitis.

on the standardized therapy. Briefly, bufexamac (Anderm®, Takeda Co. Ltd, Osaka, Japan) and half doses of alclometasone dipropionate (Almeta®, Shionogi Co. Ltd, Osaka, Japan) ointments for topical applications and hydroxyzine hydrochloride (Atarax P) for antihistamine drug were used in all patients from the observation period to the end of the study. There was no difference in the doses of those drugs between the two groups during the study period. During the total study period of 10 weeks, none of the subjects received systemic steroids. During the 8 weeks following the observation period, the ACT group received ACT supplementation during the subsequent 8 weeks at a dosage of 10 mg/kg divided into two oral doses and the standardized therapy was continued. In contrast, the control group continued the standardized therapy following the observation period. The severity of AD was determined every 2 weeks during the study period by the scoring system proposed by Kimata and Igarashi.[14] Briefly, grading of skin scores was 0–2 in ascending order of severity with respect to inflammation, lichenification and cracking, respectively. These signs were assessed on four areas of the body, that is, face, trunk, arms, legs, and the maximum possible score was 24. Scores for itching and sleep disturbance were graded 0–3 in ascending order of severity. The grading of skin scores was 0–30 (mild, less than 10 points; medium, 11–20 points; severe, more than 21 points).

Peripheral eosinophil counts, serum IgE, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels were recorded at the start and the end of the study in both groups.

Statistical analysis was by the Kruskal–Wallis and Wilcoxon rank sum tests, with statistical significance set at $P < 0.05$. Data are presented as the mean + SD.

Results

Characteristics of the patients are shown in Table 1. There were no significant differences between the two groups in sex, age, serum IgE, peripheral eosinophil counts, grading scores of AD and duration of AD. The changes in grading scores of AD during the study period are shown in Fig. 1. Total, inflammation, lichenification and cracking scores of ACT group decreased after ACT supplement (Fig. 1a–d). Itching and sleep disturbance scores of the ACT group more rapidly decreased than in those of control (Fig. 1e,f). Peripheral eosinophil counts of the ACT group significantly decreased during the study period. Changes of peripheral eosinophil counts before and after ACT supplementation were as follows: 760 ± 275 versus 525 ± 217 /μL ($P < 0.01$). In contrast, there was no statistical difference in peripheral blood eosinophils of control group during the study period (784 ± 368 *vs* 673 + 206 /μL). There was no significant decrease in serum IgE, GOT and GPT levels between the two groups. There was no obvious side-effect of ACT supplementation.

Discussion

Many researchers have reported that tannins have biologic activities, such as antitumor activity,[15–20] antioxidant activity[9,10,21,22] and anti-human immunodeficiency virus (HIV) activity.[23,24] However, the biologic effects of oral tannins remain obscure, because it is not clear whether tannins are absorbed in the intestine. Kanda *et al*. have described that ACT is a mixture of oligomeric procyanidins containing the dimer to the pentadecamer of epicatechin as a unit.[11] Hackett and Griffiths have

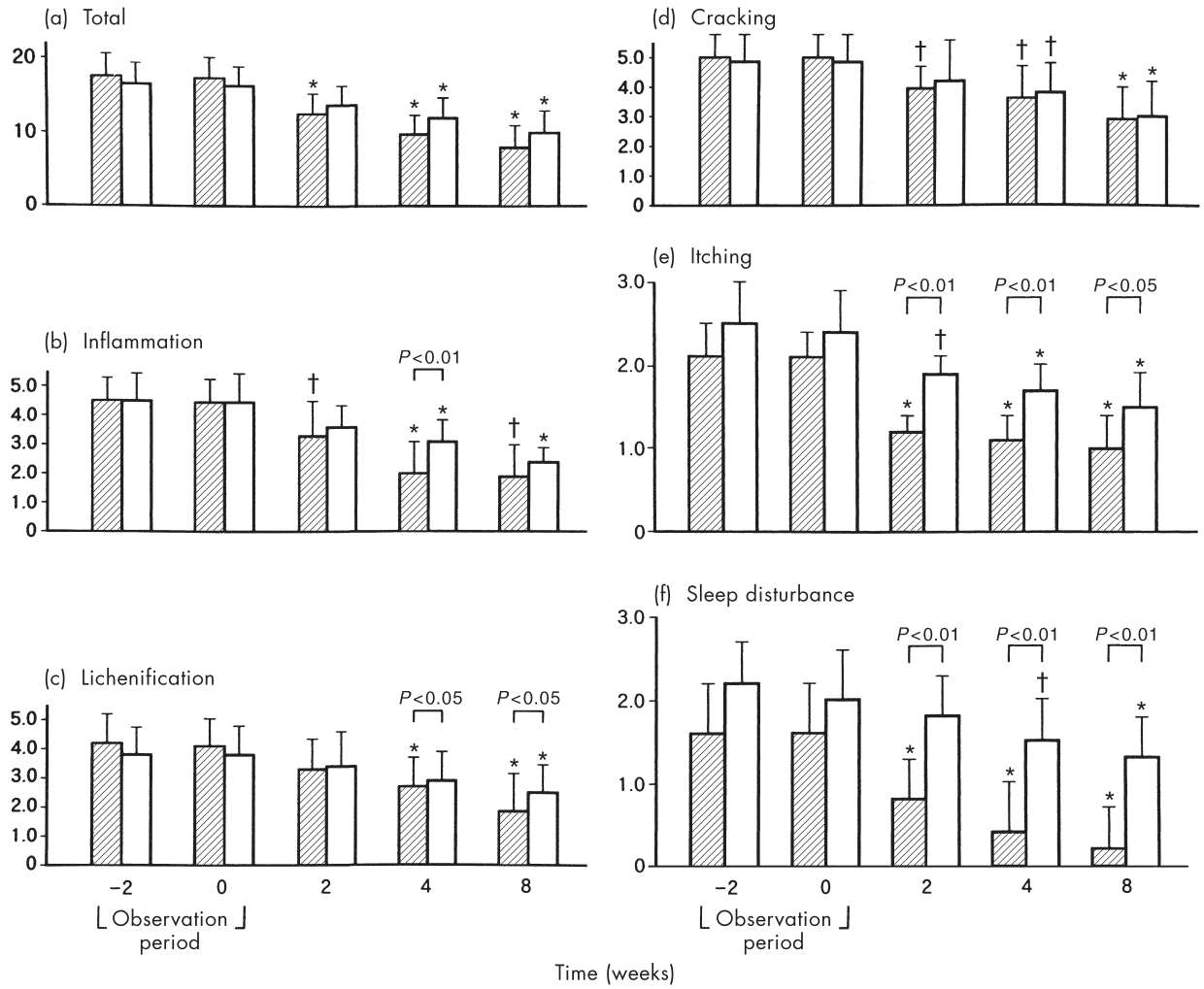

Fig. 1 Effects of apple condensed tannins (ACT) on the grading scores of total, inflammation, lichenification, cracking, itching and sleep disturbance of atopic dermatitis (a bar shows the mean ± SD). The ACT group (▨) received the ACT supplement during 8 weeks at a dosage of 10 mg/kg per day. The control group (□) continued the standardized therapy. $^{*}P < 0.01$, $^{\dagger}P < 0.05$ compared with the score at 0 weeks.

reported that orally administered catechin is absorbed and detected in the serum, liver, lung and skin in rats.[25] Das has reported that at least 10–20% of the oral catechin is absorbed and finally excreted in the urine and feces in man.[26] In the present study, we showed that ACT supplement given to the patients at a dosage of 10 mg/kg per day improved the symptomatic problems of the patients with AD. These results suggest that ACT is absorbed through the intestine and may have biologic activities *in vivo*.

Kanda *et al*. have demonstrated that ACT inhibits the histamine release from RBL2H3 cells during antigen-specific stimulation by the antigen-IgE complex with anti-dinitrophenol (DNP) IgE and DNP-bovine serum albumin (BSA).[11] Zhu *et al*. have reported that polyphenols inhibit the binding of specific radioligands to various receptors.[27] In the immediate type allergic reaction cascade, IgE sensitizes basophils and mast cells that have a specific Fc receptor for IgE on the cell surface. Therefore, it is of interest to know whether ACT affects the IgE sensitization stage in the cascade and inhibits histamine release.

It is believed that hyaluronidase plays an important role in the allergic action because some anti-allergic drugs inhibit hyaluronidase. It has been reported that ACT inhibits hyaluronidase as strongly as disodium

cromoglycate, which is one of the strongest inhibitors of hyaluronidase and is clinically used as an anti-allergic drug.[11] These observations suggest that ACT exhibits anti-allergic activity, not only as an inhibitor of histamine release, but also as an inhibitor of the enzyme that increases cell permeability.

In the present pilot study, we tried to clarify the anti-allergic effects of ACT on patients with AD. Results showed that ACT supplementation in patients with AD decreased grading scores of AD, especially in itching and sleep disturbance scores. We also observed the changes in peripheral blood eosinophil counts during the study period, because it is well known that patients with AD are frequently associated with blood eosinophilia,[28] which correlates to the activity of this disease. Blood eosinophils in patients of the ACT-supplemented group were significantly decreased when compared with before the study ($P < 0.05$). These results suggest that the decrease in peripheral eosinophil count and/or improvement in skin scores in AD patients who received ACT supplementation may be due to anti-allergic effects described by previous reports.

In conclusion, the oral administration of ACT showed a beneficial effect on patients with AD. Apple condensed tannins are therefore a recommended adjunct to the therapeutic protocol for patients with AD. Fractionation of ACT according to the polymerization number is now in progress. Further studies for the isolation of oligomers are needed to define the structural feature involved in the anti-allergic effect.

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