



## Human Skin Safety Test of Green Tea Cell Extracts in Condition of Allergic Contact Dermatitis

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Various kinds of positive effects of green tea extracts had been studied for long time which included anti-inflammation, anti-aging, and cardiometabolic effects. Although topical steroid and non-steroidal calcineurin inhibitors may control clinical symptoms of allergic contact dermatitis, some of patients also present allergic reaction to these topical agents. Therefore, we have tried green tea extracts for managing this skin disorder with expectation of anti-inflammatory effect without potential side effects including skin irritation and toxic responses. The toxicity test of green tea extract also did not show any sign of irritation in the skin throughout the test period. Moderate severity of allergic contact dermatitis presented satisfactory clinical outcome at second week follow-up which was final visit of outpatient. This result mean that green tea extract has a positive effect for managing allergic contact dermatitis but its potency and efficacy seem to be so not strong enough to control moderate severity allergy skin lesion. In this pilot study, we were able to conclude that green tea cell extracts might be applied for potential anti-inflammatory soaking without skin toxicity.

**Key words:** Green tea, Anti-inflammatory, Skin toxicity, Allergic contact dermatitis

### INTRODUCTION

Allergic contact dermatitis is a common skin disorder which is provoked by occupational chemicals including bleaching agents, hair dyeing, hand washes, plants, cosmetics, preservative, metals such as nickels or chrome. More than 3,000 allergens may attack human skin. They are spread in the world and everyone is open to its contact with allergen. If allergen provokes allergic contact dermatitis, usual clinical feature is skin inflammation with pruritus, erythematous red hues, and oozing with epidermal spongiosis when examined by histopathology.

Although topical steroid and non-steroidal calcineurin inhibitors may reduce clinical symptoms of allergic contact dermatitis, some of patients present idiopathic reaction or skin irritation to these agents. For instance, topical steroid usually suppress skin inflammation by inhibiting NF-kappaB pathway activation and normally do not evoke significant irritation in normal skin. But some of patients show

idiopathic allergic reaction to topical steroid and these strange phenomena is called 'paradoxical dermatosis'. Well-known agents producing paradoxical dermatoses are steroid, paraben preservative, and gold. In addition, steroid phobia is one of the important interfering factors which reduce patient compliance to topical steroid. Long term application of steroid is related with telangiectasis, skin atrophy, and folliculitis. So physician should use them followed by safety established protocol.

Non-steroidal calcineurin inhibitors are also different medical agents which showed anti-inflammatory effect by inhibiting calcineurin and NF-kappaB pathway without making steroid related side effects such as telangiectasia and skin atrophy.

Topical steroids and calcineurin inhibitors may reduce skin allergy related inflammation but these two agents have some problems such as steroid phobia, paradoxical dermatosis, and skin irritation. Therefore, we have tried green tea extract as a medical dressing agent which can be applied as soaking foam. Application of green tea expended from food to cosmetics. However, its potential possibility of medical application has not been studies yet. Throughout this study, we have examined potential application of green tea extract to manage skin inflammation induced by allergic contact

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**Table 1.** Scoring criteria for dermal reactions

Evaluation of dermal reactions			
Value	Erythema and eschar formation	Value	Edema formation
0	No erythema	0	No edema
1	Very slight erythema (barely perceptible), edges of area not well defined	1	Very slight edema (barely perceptible. Edges of area not well defined)
2	Slight erythema (pale red in color and edges definable)	2	Slight edema (edges of area well defined by definite raising)
3	Moderate to severe erythema (defined in color and area well defined)	3	Moderate edema (raised approximately 1 mm)
4	Severe erythema (beet to crimson red) to slight eschar formation (injuries in depth)	4	Severe edema (raised more than 1 mm and extending beyond area of exposure)
4	Total possible erythema score	4	Total possible edema score
8	Total possible primary irritation score		

dermatitis.

## MATERIALS AND METHODS

**Materials.** Ten healthy volunteers were enrolled for primary skin irritation and toxicity test in condition of normal skin evaluation. And 4 cases of allergic contact dermatitis patients (aged from 25 to 37, 2 male and 2 female patients) were enrolled for efficacy and safety test in condition of pathologic disease state which present impaired skin barrier function. Green tea extract was purified and provided by AmorePacific (Korea). Dilution method of green tea extract was challenged as 1 : 1 ratio with distilled water of 200 ml (total 400 ml for one person). Green tea extract was applied with cotton gauge soaking for 15 minutes dressing without occlusion.

**Clinical patch test.** The patch test was performed on the skin of seven men and three women, aged 20 to 40 years with Fitzpatrick skin type III to IV (Diffey, 1991). Individuals were excluded if they had any active or history of underlying chronic skin diseases that may interfere with the evaluation of skin reactions. All participants were required to sign an informed consent agreement.

The test samples (0.2 ml of 1 : 1 dilution) was placed on a Finn Chamber (Chemotechnique Diagnostics, Sweden) and applied to the ventral side of each subject's upper arm for 24 hour in an occlusive condition. Skin reactions were evaluated 1 and 24 hour after removing the test samples. The reaction was evaluated according to the International Contact Dermatitis Research Group (ISDRG) standard (Lachapelle, 1997).

**Skin irritation test.** The test procedure was done on the "Guidelines for safety test of the drugs" provided by KFDA (KFDA, 2009). The degree of dermal irritation of green tea extract was determined in human beings using the occluded dermal irritation test method as described elsewhere. Skin

irritation test were examined for the presence of erythema and edema according to the dermal irritation scoring system (Table 1) at grading intervals of 1 hour and 24 hour (Draize, 1965).

The primary irritation index (PII) was calculated by dividing the sum of erythema and edema scores of the grading intervals multiplying by the number of grading intervals. The material was then classified according to the Draize method of classification using the PII scoring as mildly irritant (PII  $\leq$  2), moderately irritant ( $2 < \text{PII} \leq 5$ ), and severe irritant (PII  $> 5$ ) (Shara *et al.*, 2005). Data on irritation are presented as visual scores based on Draize method of erythema and edema-grading system and PII was calculated.

**Allergic contact dermatitis trial (Test in damaged skin state).** Total 4 female volunteers who were refused to use steroid or had a history of allergy to non-steroidal calcineurin inhibitors were enrolled in this study. All of the volunteers refused to take oral or systemic medicine for concerning adverse effects of dermatologic medication. Three mild and one moderate degree of allergic contact dermatitis were tried with green tea extract for twice daily protocol. These treatments were repeated for 2 weeks. These new trial were different with patch test and skin irritation test in the aspect of barrier dysfunction.

## RESULTS AND DISCUSSION

We carried out skin irritation test on the 10 healthy volunteers. Edema and erythema were not recognized at 1 hour. No significant clinical finding was observed at 24 hour after opening the patch (Table 2). Erythema faded away quickly and the skin was back to normal within a short period.

The toxicity test of green tea extract also did not show any sign of irritation in the skin throughout the test period. This result is not only in agreement with our skin irritation test result in human volunteers, where the materials caused

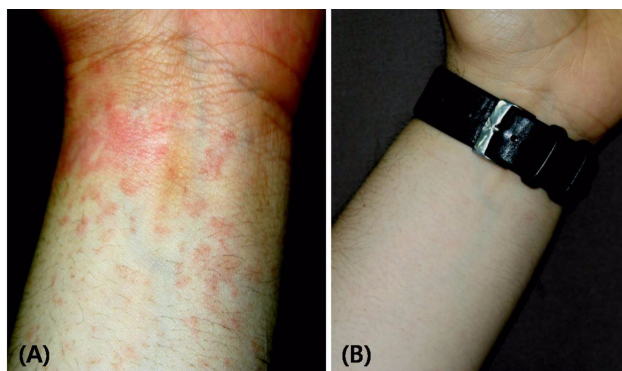
**Table 2.** Individual results of dermal irritation scoring

Patient	Age	Sex	Reaction	1 hour		24 hour	
				Intact	Abraded	Intact	Abraded
1	32	M	Erythema	0	0	0	0
			Edema	0	0	0	0
2	33	M	Erythema	0	0	0	0
			Edema	0	0	0	0
3	24	M	Erythema	0	0	0	0
			Edema	0	0	0	0
4	32	M	Erythema	0	0	0	0
			Edema	0	0	0	0
5	36	M	Erythema	0	0	0	0
			Edema	0	0	0	0
6	19	F	Erythema	0	0	0	0
			Edema	0	0	0	0
7	28	F	Erythema	0	0	0	0
			Edema	0	0	0	0
8	24	M	Erythema	0	0	0	0
			Edema	0	0	0	0
9	40	F	Erythema	0	0	0	0
			Edema	0	0	0	0
10	20	M	Erythema	0	0	0	0
			Edema	0	0	0	0

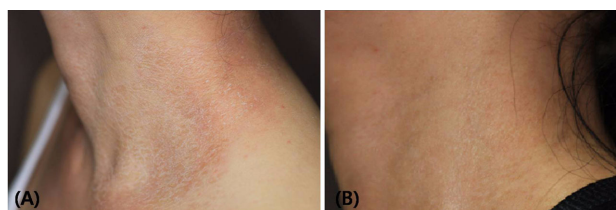
PII = 0

slightly barely perceptible erythema, but also may indicate that the degree of irritation is minimal.

Primary skin test and skin irritation test are both performed in healthy normal control skin. Therefore we could not sure if it might be applied safely for damaged skin barrier state such as allergic contact dermatitis. Therefore, we have performed 15 minutes soaking with green tea extract followed by twice daily protocol for 2 weeks. Three mild cases of allergic contact dermatitis showed marked improve-



**Fig. 1.** (A) Erythematous patches with scales on the left wrist. (B) Marked improvement of the lesion without post-inflammatory pigmentation after 1 week of green tea extract treatments.



**Fig. 2.** (A) Erythematous to light brownish patches with scales on the neck area. (B) Nearly healed state of the skin lesion after 1 week of green tea extract treatments.

ment of clinical symptom and sign of erythema and edema within first week of trial. However, moderate case of allergic contact dermatitis presented not so marked improvement at the first week of follow-up (Fig. 1 and 2). Moderate severity of allergic contact dermatitis presented satisfactory clinical outcome at second week follow-up which was final visit of outpatient. This result mean that green tea extract has a positive effect for managing allergic contact dermatitis but its potency and efficacy seem to be so not strong enough to control moderate severity allergy skin lesion. Throughout this study we can conclude that green tea extract might be applied for mild type allergic contact dermatitis. Although it potency was not so strong enough to control moderate type allergic contact dermatitis it will be able to create synergistic effect with conventional classical treatment.

Lots of positive effect of green tea extracts had been studied for long time. Most of the studies were performed *in vitro* and animal model which presented anti-inflammation, anti-carcinogenesis, anti-viral properties, new collagen synthesis, anti-diabetic, and reducing cardiovascular effect (Hara *et al.*, 1999; Matsuzaki and Hara, 1985; Xu *et al.*, 1992). In the extract of green tea, major active polyphenol catechins are epigallocatechin-3-gallate (EGCG) and epigallocatechin (EGC). These two polyphenol catechins may inhibit NF-kappaB, AKT signaling, and protein kinase C pathway so that they play various kinds of positive roles in many target organs of human (Yun *et al.*, 1996).

In conclusion, no skin reaction was observed at 1 hour and 24 hour after removing these test materials in all human subjects. Therefore, we concluded that green tea extract had minimal potential to elicit an irritation reaction. This is the first study performing green tea extract as primary skin toxicity test and clinical application for soaking type dressing agent. We believe that green tea extract can be safely utilized not only in cosmetic ingredients but also for human skin medical application.

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