

Pharmacology and therapeutics

Topical herbal extract (Huangdang mixture) exhibits both preventive and therapeutic effects in murine acute irritant contact dermatitis

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Abstract

Background Contact dermatitis, including allergic contact dermatitis and irritant contact dermatitis, are among the most common skin disorders in humans. Chinese herbal medicines (CHM) have been used in treating contact dermatitis for centuries. Systemic administration of CHM, including ingredients in Huangdang mixture containing Chinese angelica, Radix Paeoniae rubra, cat nut, and phellodendron, rhizoma alismatis, rhizoma smilacis glabrae, and rhizome of swordlike, improves allergic contact dermatitis induced by 1-fluoro-2,4-dinitrobenzene. Whether topical applications of these herbal extracts display preventive and/or therapeutic effects on contact dermatitis, thereby avoiding the potential side effects of systemic CHM, remains largely unknown.

Aims To determine whether this topical CHM extract exerts preventive and/or therapeutic effects, we assessed its efficacy in both allergic contact dermatitis and irritant contact dermatitis murine models.

Materials and methods Allergic contact dermatitis and irritant contact dermatitis murine models were established by topical oxazolone and a phorbol ester (12-O-tetradecanoylphorbol-13-acetate; TPA), respectively. Ear thickness was assessed in both dermatitis models.

Results Our results demonstrate that this topical CHM extract exhibits both therapeutic and preventive effects in acute irritant contact dermatitis but no demonstrable efficacy in murine allergic contact dermatitis.

Conclusion These results suggest that this topical CHM extract could provide an alternative regimen for the prevention and treatment of irritant contact dermatitis.

Introduction

Both allergic contact dermatitis and irritant contact dermatitis are common skin disorders in humans. Recent studies suggest that atopic dermatitis (AD) could also represent a type of chronic allergic contact dermatitis.^{1,2} The most common therapeutic approach for these disorders currently relies upon the systemic or topical application of either corticosteroids or immunomodulators. Although these medications generally improve clinical symptoms, systemic and/or local side effects can occur with prolonged use. For example, while administration of cyclosporin A reportedly increases regulatory T-cells in AD, and is effective in treating AD and allergic contact dermatitis,³⁻⁵ a number of adverse effects including rebound flares of AD status, renal dysfunction, gingival

hyperplasia, parkinsonism, leukoencephalopathy, UV-induced skin cancers, and lymphoma can occur.⁶⁻¹⁶ Tacrolimus and pimecrolimus are immunomodulators that also are effective in treating AD in both adults and children.¹⁷⁻²⁰ However, elevated cholesterol levels and hypertension have been observed with tacrolimus treatment,²¹ and possible late development of UV-induced non-melanoma skin cancers and lymphoma are important concerns.^{22,23} Moreover, recent studies demonstrated that topical tacrolimus compromises epidermal permeability barrier function, which could lead to rebound flares of AD.^{1,24} Glucocorticoids are also commonly used to treat acute allergic contact dermatitis and irritant contact dermatitis, but sustained use of these agents can induce important systemic and cutaneous side effects, such as skin atrophy, permeability barrier dysfunction, and

increased risk of skin infections.^{25–30} Furthermore, tumor necrosis factor (TNF) α inhibitors, such as infliximab, while recently shown to be effective in treating AD, can also cause serious adverse effects including meningitis, development of psoriasiform and lichen planus-like lesions, and increased risk of lymphomas.^{31–37} Thus, substantial risks coupled with modest efficacy limit current usage of anti-inflammatory and immunomodulators for the treatment of inflammatory dermatoses, providing a rationale for the identification of effective, relatively safe and inexpensive alternative treatments for acute allergic contact dermatitis and irritant contact dermatitis.

Chinese herbal medicines (CHM), which have been used for centuries as systemic treatment of skin diseases, including allergic contact dermatitis, irritant contact dermatitis, and AD, are both inexpensive and widely available. Not only have some controlled clinical studies shown that systemic administration of CHM comprises an effective, safe, and inexpensive treatment for these dermatoses,^{38–40} but also in murine models, systemic administration of CHM prevents development of AD.^{41–44} However, in comparison with topical therapy, systemic treatment with CHM usually requires higher dosages of these extracts, which increase both cost and the probability of toxicity. Data about efficacy of topical applications of CHM in acute allergic contact dermatitis and irritant contact dermatitis are few. We therefore assessed here whether topical CHM exerts preventive and/or therapeutic benefits in either an acute allergic contact dermatitis or an irritant contact dermatitis murine model. We utilized a CHM, Huangtang mixture, in which ingredients have been shown previously to exert beneficial effects on contact dermatitis.⁴⁵

Materials and methods

Materials

Six to eight-week-old female C57BL/6J mice were purchased from Charles River Laboratories (Wilmington, MA, USA) and fed mouse diet (Ralston-Purina, St Louis, MO, USA) and water *ad libitum*. 12-*O*-Tetradecanoylphorbol-13-acetate (TPA), oxazolone and acetone were purchased from Sigma Chemical (St Louis, MO, USA). Herbal mixture (Huangtang) extract was made by soaking the mixture of Chinese angelica, Radix Paeoniae rubra, cat nut, phelloden dron, rhizoma alismatis, rhizoma smilacis glabrae, and rhizome of swordlike in 100% ethanol for three weeks. The ethanol extract was used as the treatment agent.

Experimental protocols

All animal procedures were approved by the Animal Studies Subcommittee of the San Francisco Veterans Administration Medical Center and performed in accordance with their

Table 1 Effect of topical herbal mixture on inflammatory response in acute irritant contact dermatitis

	Ear thickness (mm)	
	Experiment 1 (n = 6)	Experiment 2 (n = 10)
Normal	0.248 $\pm$ 0.006	0.205 $\pm$ 0.002
0.03% TPA + Vehicle	0.667 $\pm$ 0.027	0.387 $\pm$ 0.025
0.03% TPA + Mix	0.597 $\pm$ 0.027	0.265 $\pm$ 0.015
Significances		
Normal vs. Vehicle	$q = 24.69, P < 0.001$	$q = 14.23, P < 0.001$
Normal vs. Mix	$q = 20.56, P < 0.001$	$q = 4.717, P < 0.01$
Vehicle vs. Mix	$q = 3.578, P < 0.05$	$q = 8.238, P < 0.001$

TPA, 12-*O*-tetradecanoylphorbol-13-acetate.

guidelines. For anti-inflammatory studies in irritant contact dermatitis model, a total of 48 mice were used (detailed in Table 1). Ear inflammation on C57BL/6J mice was induced by topical application of 15 μ l of 0.03% TPA to both inner and outer surfaces of both ears.^{46,47} Twenty microliters of 1% Huangtang extract in ethanol or ethanol alone was applied to both surfaces of the right or left ear at 45 minutes and four hours following TPA treatment. Additionally, the oxazolone-induced ear inflammation model (allergic contact dermatitis model) on a total of 60 mice was also used to assess the anti-inflammatory effects of Huangtang mixture. C57BL/6J mice were sensitized by topical application of 3% oxazolone to the back once daily for two days. One week later, 15 μ l of 0.5% oxazolone was applied to both inner and outer surfaces of both ears. Twenty microliters of 1% Huangtang or ethanol alone was applied to both surfaces of the right or left ear at 45 minutes and four hours following oxazolone treatment. Ear thickness was measured with a digital caliper (Mitutoyo, Tokyo, Japan) before and 20 hours after challenge with oxazolone or TPA application, and samples were taken for H&E staining.

For the prevention study, one group of mouse ears was treated with either 20 μ l of 1% Huangtang or ethanol alone twice daily for seven days before the irritant contact dermatitis or allergic contact dermatitis model was established. Another group of mouse ears was treated only once with 1% Huangtang. TPA and oxazolone challenge were performed 18 hours after the last herbal mixture or ethanol application. No Huangtang or ethanol was applied after TPA or oxazolone challenge.

Statistics

Data are expressed as the mean + SEM. GraphPad prism 4 software was used for all statistical analyses. Unpaired two-tailed Student's *t*-test with Welch's correction was used to determine the statistical significances when two groups were compared. One-way ANOVA test with Tukey correction was used to determine significant differences when three or more groups were compared.

Results

Pretreatment with CHM extract reduces inflammation in acute irritant, but not in allergic contact, dermatitis

Previous studies have demonstrated that systemic administration of Huangdang reduced inflammation in the murine allergic contact dermatitis model.⁴⁸ Hence, we first assessed whether topical applications of the Huangdang extract prevent the development of either acute irritant and/or allergic contact dermatitis. The gross appearance of mouse ears remained normal after seven days of topical Huangdang treatment alone, and histologically there was no sign of toxicity following topical Huangdang treatment. As shown previously,^{45,46} topical TPA treatment alone caused a significant increase in ear thickness in mice pretreated with vehicle alone (Fig. 1a). While ear thickness was not reduced in mice pretreated once with Huangdang (Fig. 1a), pretreatment with Huangdang for seven days caused a significant reduction in ear thickness as compared with either vehicle alone or mice pretreated only once with Huangdang (Fig. 1a). Yet, in contrast to the acute irritant

contact dermatitis model, pretreatment with topical Huangdang extract did not reduce inflammation in the acute allergic contact dermatitis model (Fig. 1b). These results indicate that topical Huangdang extract prevents the development of acute irritant contact dermatitis.

Topical CHM extract reduces inflammation in acute irritant, but not in acute allergic contact, dermatitis

We next tested whether the topical Huangdang extract decreases cutaneous inflammation in either acute irritant contact dermatitis and/or allergic contact dermatitis models. Acute irritant contact dermatitis model was established by topical application of 15 μ l of 0.03% TPA, and 20 μ l of Huangdang extract was applied 45 minutes and four hours following TPA treatment. Data from two separate experiments demonstrate that topical applications of Huangdang extract reduced ear inflammation significantly compared with vehicle treatment alone in the acute irritant contact dermatitis model (Table 1; Fig. 2b vs. c; Fig. S1). However, no differences in ear thickness were found between CHM extract and vehicle treatment in the acute allergic contact dermatitis model (Table 2; Fig. 2e vs. f; Fig. S1). These results suggest that topical Huangdang extract exhibits therapeutic benefits for the treatment of acute irritant contact dermatitis but not acute allergic contact dermatitis.

Discussion

CHM have been used widely for the treatment of inflammatory dermatoses in China for millennia. A number of studies have demonstrated that systemic administration of CHM benefit eczema/AD.^{49–52} Additionally, the development of allergic contact dermatitis and AD-like lesions in murine models are inhibited by oral CHM.^{53–55} Moreover, our previous studies showed that another CHM, topical Tuhuai extract, inhibits both acute irritant contact dermatitis and allergic contact dermatitis in the same murine models employed here.⁵⁶ Furthermore, ingredients in the Huangdang mixture also show benefits for inflammatory dermatoses in both human and murine models.^{57–60} Our present results show that topical applications of Huangdang extract exhibit both preventive and therapeutic effects in acute irritant contact dermatitis. The exact mechanisms by which topical Huangdang extract alleviates inflammation are not clear. However, other studies showed that both rhizoma smilacis glabrae and Paoniae alba Radix extract, ingredients in the Huangdang mixture, reduced TNF α and interleukin (IL)-1 α levels in an arthritis model.^{61–63} Likewise, Chinese angelica, another ingredient in the Huangdang mixture, suppresses radiation-induced expression of TNF α and transforming growth factor- β 1 in mouse lung.⁶⁴ Moreover, prior *in vitro* studies

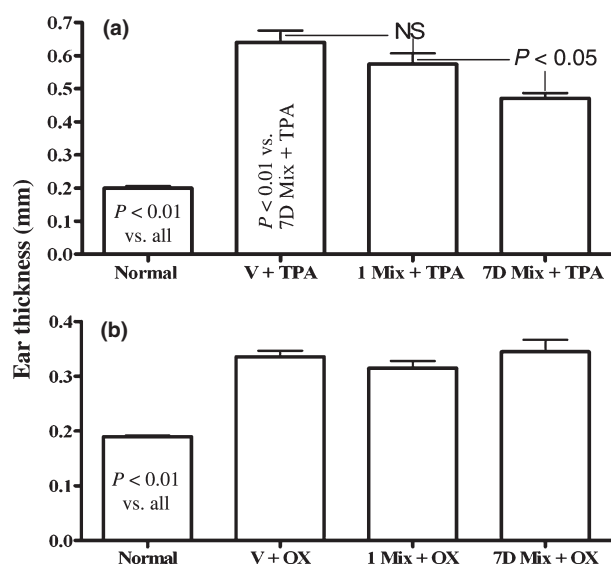


Figure 1 Effects of pretreatment with Huangdang extract on cutaneous inflammatory response in acute irritant contact dermatitis and allergic contact dermatitis models. Mouse ears were treated topically with either vehicle or 1% Huangdang extract twice daily for 7 d. An additional group of control ears was treated with 1% Huangdang extract once, 18 h before either TPA or oxazolone challenge application, labeled as 1 Mix + TPA in (a) and 1 Mix + OX in (b), respectively. (a) Changes in ear thickness in acute irritant contact dermatitis model. (b) Changes in ear thickness in acute allergic contact dermatitis model. One-way ANOVA test, with Tukey correction, was used to determine significant differences. All significances are indicated in the figure

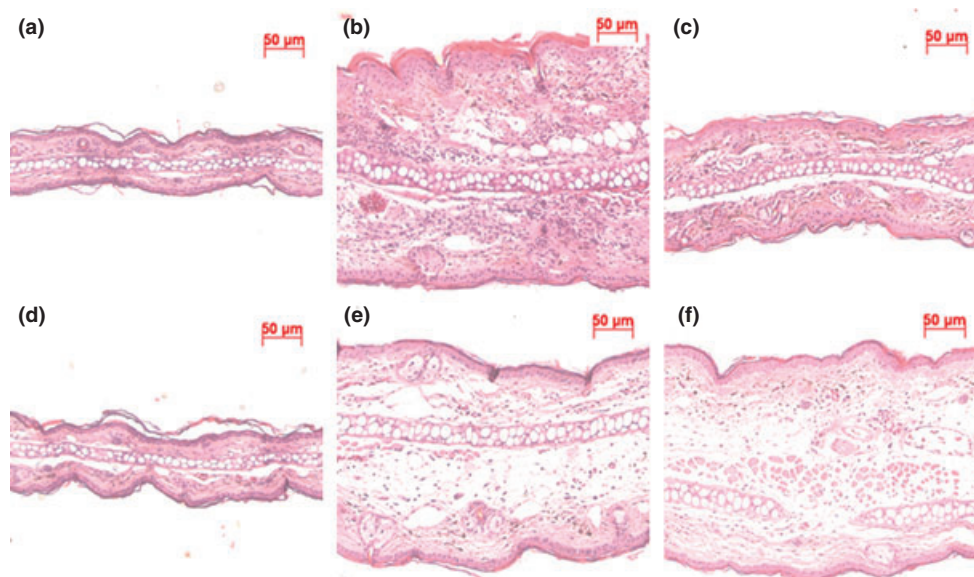


Figure 2 Topical applications of Huangdang extract reduce cutaneous inflammatory response in acute irritant contact dermatitis, but not in allergic contact dermatitis mice. Acute irritant contact dermatitis and allergic contact dermatitis models were established as described in Materials and Methods. Twenty microliters of 1% Huangdang in ethanol or ethanol alone was applied to both surfaces of the right or left ear, respectively, 45 min and 4 h following TPA or oxazolone challenge. Ear thickness was measured with a digital caliper (Mitutoyo) before and 20 h after challenge with oxazolone or TPA application, and samples were taken for H&E staining. (a and d) Normal ears. (b) Acute irritant contact dermatitis treated with vehicle. (c) Acute irritant contact dermatitis treated with Huangdang extract. (e and f) Acute allergic contact dermatitis treated with vehicle and Huangdang extract, respectively. The magnifications for all images are the same. Scale bar: 50 µm

Table 2 Effect of topical herbal mixture on inflammatory response in acute allergic contact dermatitis

	Ear thickness (mm)	
	Experiment 1 (n = 10)	Experiment 2 (n = 10)
Normal	0.201 ± 0.003	0.214 ± 0.003
0.5% OX + Vehicle	0.368 ± 0.024	0.394 ± 0.016
0.5% OX + Mixture	0.434 ± 0.030	0.396 ± 0.014
Significances		
Normal vs. Vehicle	$q = 9.397, P < 0.001$	$q = 19.24, P < 0.001$
Normal vs. Mix	$q = 13.10, P < 0.001$	$q = 19.46, P < 0.001$
Vehicle vs. Mix	$q = 3.301, P > 0.05$	$q = 0.1852, P > 0.05$

OX, oxazolone.

demonstrated that ligustilide, a compound in Chinese angelica, inhibits inflammation induced by lipopolysaccharide through inhibition of NF-κB pathway,⁶⁵ which could provide another mechanism by which the Huangdang mixture benefits inflammation. Furthermore, both 13β,17β-epoxy alisol A and alisol B 23-acetate, compounds extracted from rhizoma alismatis contained in the Huangdang mixture, exhibit dose-dependent inhibition on T-cell proliferation.⁶⁶ Therefore, reduction of TNFα and

IL-1α expression could account for the Huangdang mixture's improvement in inflammation.

Some herbal medicines have been reported to contain glucocorticoids, which are potent anti-inflammatory agents for allergic contact dermatitis.⁶⁷ However, Huangdang treatment does not reduce inflammation in acute allergic contact dermatitis. Thus, the beneficial effects of the Huangdang extract on acute irritant contact dermatitis likely cannot be attributed to any active glucocorticoid-like constituent in the extract. Moreover, the preventive effects of Huangdang extract on irritant contact dermatitis are unlikely to be attributed to any chemical and/or physical interaction of Huangdang extract with TPA, which would interfere with TPA penetration, as single application of Huangdang extract did not alter inflammatory responses. Our work differs from a previous study that showed benefits from systemic administration of a water extract of ingredients contained in Huangdang in acute allergic contact dermatitis model.⁴⁸ The discrepancy in these results could be due to different preparation methods. An ethanol, rather than an aqueous, extract was used in the present study. Thus, it is possible that the active compounds that inhibit allergic contact dermatitis are lost by ethanol extraction.

Although some prior studies suggest CHM prevent AD or allergic contact dermatitis,^{51,68} the preventive or

therapeutic effects of many CHM on dermatoses have not been well differentiated due to a lack of proper research design and choice of animal models. Without knowing whether CHM display the preventive or therapeutic effects could delay appropriate treatment and unnecessarily increase costs as well as adverse effects. Hence, it is important to know whether CHM display preventive and/or therapeutic benefits. In the present study, we used different treatment approaches and animal models to identify the preventive and/or therapeutic benefits of topical Huangdang extract in acute irritant and allergic contact dermatitis. Deployment of the approach used here could help to identify whether topical CHM directly interfere with the penetration of disease-causative agents into skin or affect on other cutaneous biological functions, which, in turn, reduce inflammation. The dermatitis models used in the present study are reproducible, easy to establish, and represent two of the most common inflammatory dermatoses. In summary, coupling these dermatitis models with treatment methods, such as the one used in this study, could help with further development of alternative topical medications for inflammatory dermatoses.

In conclusion, the present study demonstrated that: (i) topical Huangdang exhibits both preventive and therapeutic effects on acute irritant contact dermatitis, potentially it could be an alternative regime in both preventing and treating acute irritant contact dermatitis; (ii) the treatment approaches and murine dermatitis models, which are reliable and easy to be established, employed here are useful in distinguishing preventive and therapeutic effects of topical agents for contact dermatitis.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Topical applications of Huangdang extract reduce cutaneous inflammatory response in acute irritant contact dermatitis, but not in allergic contact dermatitis model.

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