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Effectiveness and safety of combination treatment of herbal medicines and oral antihistamines for atopic dermatitis: a retrospective chart review

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ABSTRACT

Background: Patients with atopic dermatitis (AD) exhibit various symptoms, especially itching. Recently, herbal medicines (HMs) are being used in combination with antihistamines for the treatment of AD in Korea. While oral antihistamines can alleviate itching, HMs appear to exert anti-inflammatory effects with minimal side effects. However, there is little evidence regarding the effectiveness and safety of using HMs in combination with antihistamines for AD.

Methods: To observe the effectiveness and safety of combination treatment with HMs and antihistamines, we performed a retrospective chart review of inpatients with AD who received this combination treatment for at least 7 days in a hospital.

Results: Of 163 inpatients, 40 met the inclusion criteria. All patients received HMs three times, and one or two antihistamines, a day after HM intake. A large proportion of patients received first-generation antihistamines. HMs comprised a mixture of an average of 20.69 different herbs in decoction. The mean total, objective, and subjective SCORing Atopic Dermatitis scores showed a significant decrease after combination treatment. Changes in the mean levels of aspartate transaminase, alanine transaminase, blood urea nitrogen, and creatinine were not statistically significant among treatments. There were no adverse events of pseudoaldosteronism or interstitial pneumonia.

Conclusion: We observed that the short-term use of HMs in combination with oral antihistamines was safe and effective, with a low risk of adverse reactions. This study was limited by its retrospective design, and prospective studies with long-term follow-up periods are warranted to further elucidate the safety of this combination treatment for AD.

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1. Introduction

Atopic dermatitis (AD) is a common pruritic inflammatory skin disease with an increasing prevalence in industrialized countries. The worldwide prevalence of AD is 5–20%.[1] AD is characterized by pruritus, eczematous lesions accompanied by excessive infiltration of inflammatory cells, eosinophilia in the peripheral blood, and high levels of serum immunoglobulin E (IgE).[2]

Inflammatory skin changes accompanying itching are the most important manifestations of AD. Therefore, treatment should address the epidermal barrier as well as immunomodulation or infection; AD treatment typically includes anti-inflammatory agents, antipruritic agents, and occasionally, antiseptic agents.[3]

Antihistamines are frequently used for the management of itching in AD. This class of drugs can block H1 receptors on afferent C nerve fibers and inhibit the release of pruritic mediators.[4] Antihistamines exhibit several adverse side effects related to their antihistaminic actions. However, these are usually mild and can be rapidly reversed with the discontinuation of treatment or a decrease in the dose.[5] Their relative safety probably relates to their use in low doses for a short time period.

Herbal medicines (HMs) are medicinal plants used for the prevention and treatment of disease. In East Asia, herbs are widely used for the treatment of AD because of their efficacy and minimal side effects. Several studies have provided scientific evidence for the clinical efficacy and safety of HMs for the treatment of AD.[6–8]

HMs and conventional treatments are generally prescribed independently for AD; however, for some patients with uncontrolled itching, these agents are routinely combined in clinical practice for faster relief from itching. However, no study has evaluated the combined use of HMs and oral antihistamines for AD. Therefore, we performed a retrospective chart review to observe the safety and effectiveness of short-term combination therapy with HMs and oral antihistamines for inpatients with AD in Seoul, Republic of Korea.

2. Methods

2.1. Patients and study design

We conducted a retrospective chart review of inpatients treated at the Department of Dermatology of Korean Medicine, Kyung Hee University Hospital, Seoul, Korea, between January 2011 and May 2016. Using electronic medical records (EMRs, NeoMed, Hyundai Information Technology, Seoul, South Korea), patients were selected on the basis of the following criteria.

The inclusion criteria were as follows: hospitalization for AD; combined use of HMs and oral antihistamines for at least 7 days; availability of SCORing Atopic Dermatitis (SCORAD) scores, total serum IgE level data, and eosinophil counts before and after treatment; availability of results of blood tests for the evaluation of liver and renal function before and after treatment; and access to medical records of adverse events, including pseudoaldosteronism and interstitial pneumonia. The exclusion criteria were as follows: use of systemic steroids, immunosuppressants, and antibiotics during hospitalization; and use of topical steroids and calcineurin inhibitors during hospitalization. This study was approved by the Institutional Review Board of Kyung Hee University Hospital (KHNMC-OH-IRB 2014-05-003).

2.2. Combination treatment

Data regarding patient demographics and treatment regimens were collected from EMRs, with a focus on HM prescriptions and antihistaminic use. We also reviewed individual patients who received herbs with previously reported potential for hep-

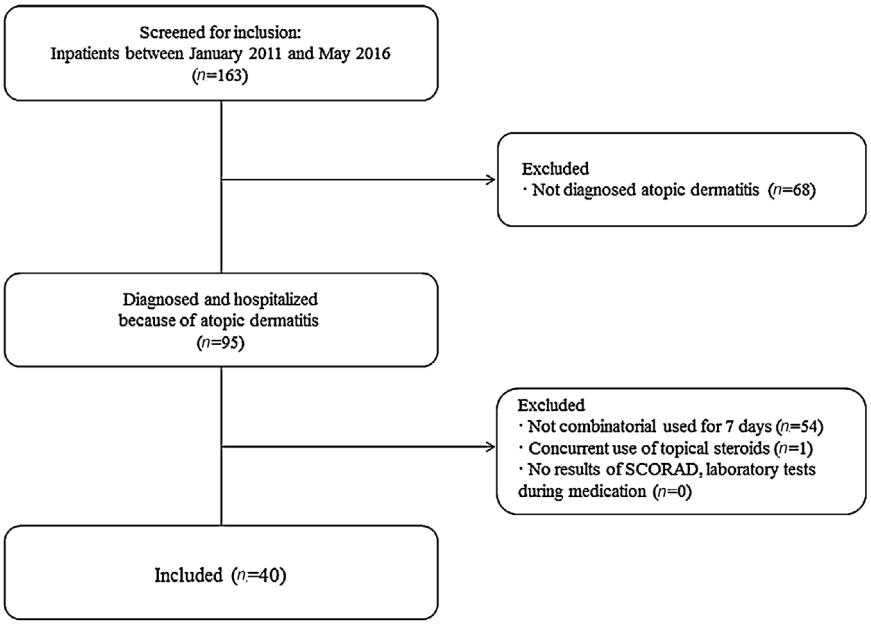

Fig. 1 – Selection process of retrospective chart review. **SCORAD, SCORing Atopic Dermatitis.**

Table 1 – Herbs with previously reported potential for hepatotoxicity, pseudoaldosteronism, or interstitial pneumonia.

	Name of herb
Hepatotoxicity	*Radix Polygoni multiflori*
	Turcz Dictamnus dasycarpus
	Cortex Ulmus davidiana
	Radix Puerariae
	Fructus Psoraleae
	Aloe Vera
	Cortex Cudraniae
	Ceramium kondoi
	Radix Smilacis chinae
	Corydalis speciosa Max
Pseudoaldosteronism	*Radix Glycyrrhizae*
Interstitial pneumonia	*Radix Scutellariae*
	Radix Bupleuri

atotoxicity, pseudoaldosteronism, or interstitial pneumonia (Table 1).[9–11]

2.3. *Assessment of effectiveness and safety*

To observe the effectiveness and safety of combination treatment, we assessed the SCORAD score; total serum IgE level; eosinophil count; levels of aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), and creatinine; and adverse events, including pseudoaldosteronism and interstitial pneumonia.

2.4. *Statistical analyses*

We analyzed the collected data using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation or number (%). The paired t test was used to evaluate statistically significant changes in SCORAD score; total serum IgE level; eosinophil count; and AST, ALT, BUN, and creatinine levels after treatment. A p value < 0.05 was considered statistically significant.

Table 2 – Clinical characteristics of 40 patients who received combination treatment with herbal medicines and oral antihistamines.

Patient characteristics	
Sex (M/F)	14/26
Age, y	21.7 (2–38)
Children (2–19 y)	18
Adults (over 19 y)	22
Body weight, kg	54.7 (12.0–78.5)
Duration of AD, y	7.6 (0.17–20)
Duration of admission, d	12.7 (8–26)
Duration of combination treatment, d	11.7 (7–18)

AD, atopic dermatitis; F, female; M, male.
Data are presented as *n* or mean (range).

3. Results

3.1. *Patient selection and characteristics*

We collected patient data from EMRs dated between January 2011 and May 2016. During the study period, 95 of 163 inpatients were diagnosed with and hospitalized for AD. Among these, 40 patients fulfilled all the inclusion and exclusion criteria (Fig. 1). The clinical characteristics of patients on the day of admission are summarized in Table 2. All patients were younger than 38 years. Their body weights were very diverse. The mean durations of admission and combination treatment were 12.7 days and 11.7 days, respectively.

Table 3 – Types of antihistamines prescribed for relief from itching caused by atopic dermatitis.

Case (*n*)	Age (y)	Type of antihistamines	Dosage	Duration (d)
24	11–38	Hydroxyzine HCl only	5–20 mg	7–26
3	10, 21	Pseudoephedrine HCl & Triprolidine HCl	30 mg, 1.25 mg	8, 18
	28		60 mg, 2.5 mg	7
2	26	Hydroxyzine HCl, Ebastine	10 mg, 10 mg	14
	38		30 mg, 10 mg	13
2	6	Hydroxyzine HCl → Pseudoephedrine HCl & Triprolidine HCl	6 mg→ 30 mg, 1.25 mg	7(2 → 5)
	7			
2	15	Cetirizine HCl	10 mg	9
	19			10
1	18	Hydroxyzine HCl → Hydroxyzine HCl, Ebastine	10 mg→ 20 mg, 10 mg	11 (2 → 9)
1	31	Hydroxyzine HCl, Bepotastine besilate → Hydroxyzine HCl only	10 mg each	7 (5 → 2)
1	22	Ebastine, Bepotastine besilate	10 mg each	18
1	32	Hydroxyzine HCl, Cetirizine HCl	10 mg each	11
1	21	Ebastine, Levocetirizine HCl	10 mg, 5 mg	10
1	7	Mequitazine	4 mg	10
1	2	Ketotifen Furamate	1.38 mg	11

Bepotastine besilate, Talion; Cetirizine HCl, Zyrtec; Ebastine, Ebastel; Hydroxyzine HCl, Ucerax; Ketotifen Furamate, Ketotifen; Levocetirizine HCl, Letirizine; Mequitazine, Primalan; Pseudoephedrine HCl & Triprolidine HCl, Actifed.

Table 4 – Eleven most commonly used herbs for the 40 patients included in this study.

Scientific name	Patient number (*n*)	Used dose (g/d)
Radix Rehmanniae	38	37.90 (8–60)
Radix Glycyrrhizae	35	10.82 (4–12)
Akebiae caulis	33	12.00 (8–16)
Radix Astragali	32	16.50 (4–24)
Rhizoma Atractylodis	31	12.52 (8–20)
Radix Scutellariae	31	11.4 (4–12)
Rhizoma Smilacis	30	12.97 (12–20)
Radix Angelicae gigantis	28	10.79 (8–16)
Radix Adenophorae	28	14.43 (12–16)
Radix Gentianae scabrae	28	12.14 (12–16)
Semen Plantaginis	28	12.00 (8–16)

Data are presented as mean (range).

Table 5 – Patients who received herb(s) with previously reported potential for hepatotoxicity, pseudoaldosteronism, or interstitial pneumonia.

	Patient number (*n*)	Used dose (g/d)
Radix Polygoni multiflori	1	4
Turcz Dictamnus dasycarpus	3	10.67 (8–12)
Cortex Ulmus davidiana	0	0
Radix Puerariae	8	13 (12–16)
Fructus Psoraleae	0	0
Aloe Vera	0	0
Cortex Cudraniae	2	10 (8–12)
Ceramium Kondoi	0	0
Radix Smilacis chinae	30	12.97 (12–20)
Corydalis speciosa Max	0	0
Radix Glycyrrhizae	35	10.82 (4–12)
Radix Scutellariae	31	11.4 (4–12)
Radix Bupleuri	18	8.96 (6–16)

Data are presented as mean (range).

3.2. *Combination treatment with HMs and oral antihistamines*

All patients received HMs thrice a day after meals and one or two antihistamines once or twice a day within 30 minutes after HM intake. Among the 40 included patients, 31 received one type of antihistamine, 5 received two different types, and 4 received altered types due to a lack of relief from itching. A large proportion of patients received first-generation antihistamines. Details of the treatment regimens are summarized in Table 3.

HMs comprised a mixture of an average of 20.69 different herbs in decoction. A total of 98 different herbs were used for the 40 patients. The mean dry mass of HM per patient was 259.82 g/d. The 11 most commonly used herbs are listed in Table 4. From the 13 herbs listed as potentially causing hepatotoxicity, pseudoaldosteronism, or interstitial pneumonia in Table 1, *Radix Glycyrrhizae* was prescribed to 35 patients, *Radix Scutellariae* to 31, *Rhizoma Smilacis* to 30, *Radix Bupleuri* to 18, *Radix Puerariae* Radix to eight, *Turcz Dictamnus dasycarpus* to three, *Cortex Cudraniae* to two, and *Radix Polygoni multiflora* to one (Tables 4 and 5).

3.3. *Concomitant medications*

Included patients sometimes used emollients and lotions. In addition, an ointment that contains herbs was used during hospitalization. Jawoongo (Shiunko in Japanese), which is composed of *Radix Angelicae gigantis* and *Radix Lithospermi*, was used for excoriation, lichenification, and dryness.[12,13]

3.4. *Assessment of effectiveness and safety*

The mean total, objective, and subjective SCORAD scores showed a significant decrease after combination treatment ($p < 0.001$). However, total serum IgE level increased and eosinophil counts decreased slightly, but the changes in the two values were not clinically meaningful when considering the reference range. Moreover, changes in the mean levels of AST, ALT, and creatinine after treatment were not statistically significant ($p > 0.05$). Levels of BUN also slightly decreased, but the change was not clinically meaningful when considering the reference range. The results are summarized in Table 6 and Fig. 2. There were no adverse reports of pseudoaldosteronism or interstitial pneumonia.

4. Discussion

HMs are widely used in many countries, particularly East Asian countries, for the treatment of AD. Some herbs have exhibited anti-inflammatory effects in human studies.[14] In more recent randomized, placebo- or active drug-controlled studies on HMs, Xiao-Feng-San, TJ-15, and TJ-17 resulted in significantly improved clinical symptom scores and pruritus scores.[6,15] Furthermore, some individual herbs that benefit AD patients include St John's wort, licorice, and mahonia.[16–18] The most commonly proposed mechanism of HMs is an anti-inflammatory effect through suppression of the Th2 response and/or modulation of the Th1 response.[19]

For AD patients with uncontrolled itching, combination treatment with HMs and oral antihistamines is routinely employed in clinical practice in Korea. Antihistamines are frequently used for the management of itching in AD. Antihistamines exhibit several adverse side effects related to their antihistaminic actions, including sedation, impaired motor function, dizziness, dry mouth and throat, blurred vision, urinary retention, and constipation. However, these side effects are usually mild and can be rapidly reversed with discontinuation of treatment or a decrease in dose.[5] Antihistamines rarely cause liver injury. Their relative safety probably relates to their use in low doses for short time periods.[20]

HMs also exhibit some side effects, including hepatotoxicity, pseudoaldosteronism, and interstitial pneumonia, which may occasionally arise after treatment in certain patients.[9–11] According to previous studies, the incidence of HM-induced liver injury is less than 1%,[21] and it is related to prolonged dosing and/or overdose of certain herbs such as *Radix Polygoni multiflori*.[22] Prolonged use of excessive doses of *Radix Glycyrrhizae* can lead to pseudoaldosteronism, which includes potassium depletion, sodium retention, edema, hypertension, and weight gain. However, it may occur when an herb is used

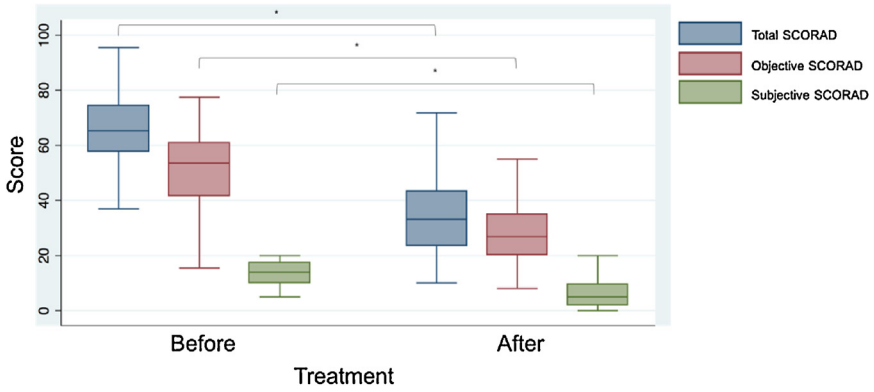

Fig. 2 – Changes in SCORing Atopic Dermatitis scores after combination treatment with herbal medicines and oral antihistamines.
SCORAD, SCORing Atopic Dermatitis.
***p < 0.05 by paired t test.**

Table 6 – Effectiveness and safety outcomes for combination treatment with herbal medicines and oral antihistamines for atopic dermatitis.

	Before treatment	After treatment	Reference range	*p*
	Mean ± SD			
Total SCORAD score (0–103)	64.4 ± 15.2	34.8 ± 14.5		<0.0001*
Objective SCORAD score (0–83)	50.8 ± 13.7	28.5 ± 11.6		<0.0001*
Subjective SCORAD score (0–20)	13.7 ± 4.4	6.3 ± 4.9		<0.0001*
Eosinophil count	1310.3 ± 1816.4	1099.2 ± 1580.7	30–350/μL	0.039*
Serum total IgE level	2320.2 ± 2672.4	2483.3 ± 2935.1	<100 IU/mL	0.155
AST level	26.5 ± 8.7	25.3 ± 7.1	<40 U/L	0.408
ALT level	18.9 ± 11.1	19.8 ± 9.6	<40 U/L	0.628
BUN level	10.2 ± 3.0	9.0 ± 2.2	8–20 mg/dL	0.023*
Creatinine level	0.7 ± 0.17	0.63 ± 0.18	0.5–0.9 mg/dL	0.058

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; IgE, immunoglobulin E; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.
* Using paired *t* test.

for more than 6 weeks or when taken in excessive doses over 50 g/d.[23] There are few studies regarding interstitial pneumonia associated with *Radix Scutellaria baicalensis* and *Radix Bupleuri* and/or interferon.[10] However, these studies have been reported in patients with hepatitis.

Despite the common combinational use of HMs and conventional medicine, studies documenting the efficacy and safety of these combinations are sparse. One review article describing interactions between herbs and prescribed drugs showed that specific herbs such as St John's wort, gingko, and ginseng interact with certain drugs such as warfarin, aspirin, and cyclosporine.[29] In that review, herbal mixtures, antihistamines, and patients with skin disease were not included.

A recent study showed that combinatorial use of oral herbal medication with conventional treatment reduced exposure to corticosteroids among children with AD in Taiwan.[24] In Japan, Sipmipaedoksan (Jumihaidokuto in Japanese, Shiweibadusan in Chinese), a Kampo formula, decreases the disease activity of palmoplantar pustulosis when used with topical corticosteroids and oral antihistamines.[25] However, few reported studies regarding the combinatorial use of HMs and oral antihistamines for AD have been published in the English literature. As we discussed above, both HMs and oral antihistamines are relatively safe under careful and professional medical practice. Furthermore, AD patients are usually young, with a liver function that does not differ from that of healthy people. In the 1990s, a few studies claimed a relationship between AD and abnormal liver function in infants. To the best of our knowledge, there are no reports showing that liver function is more vulnerable in AD patients than in healthy people.

During the study period, 40 of 163 inpatients fulfilled the inclusion criteria. Similar to a recent study,[26] all patients were younger than 38 years. The mean durations of admission and combination treatment were 12.7 days and 11.7 days, respectively. All patients received HMs three times after meals and one or two antihistamines once or twice a day within 30 minutes after HM intake. HMs comprised a mixture of an average of 20.69 different herbs, and a total of 98 different herbs were used for the included patients. The most commonly used herbs, including *Radix Rehmanniae* and *Radix Glycyrrhizae*, are listed in Table 4. Except *Radix Rehmanniae*, the dose range for each herb in a decoction is 10–16 g. For the majority of commonly used herbs, the range is 6–15 g for a 1-day dose. Some herbs like *Radix Rehmanniae* are used at considerably higher dosages for a decoction, whereas some herbs

are used in much lower dosages due to their side effects or toxicity.[27] In this study, because many patients received herbs with the potential for hepatotoxicity, pseudoaldosteronism, or interstitial pneumonia, the herbs were dosed at less than 20 g/d.

The mean objective SCORAD score decreased from 50.8 to 28.5 during 11 days of the combination treatment. Depending on the classification of severity of AD, < 15 objective SCORAD score are mild, 15–40 are moderate, and > 40 are severe.[28] In this study, the mean score of objective SCORAD score decreased from severe to moderate. The changes in SCORAD scores observed in the present study were similar to those observed in a previous study by the authors, which was a retrospective chart review of inpatients with severe AD.[8] In that study, the objective SCORAD score of 29 patients was reduced from 48.38 to 30.46 during an average of 9.79 days of inpatient treatment with herbal medicines, acupuncture, and herbal wet wrap dressing. Among the 29 patients of the previous study, 5 used antihistamines. Antihistamines are selectively used when itching is not controlled.

However; eosinophil counts statistically significant decreased, and serum total IgE level slightly increased, but not all of them were clinically meaningful changes considering the reference range. Although elevated serum total IgE levels and eosinophil counts have been reported in AD patients, also these may reflect the severity of AD or may play as prognostic factors, there are yet many opinions that are opposed. In addition, the study period of 12.7 days could be short to change the hematology results.

In the present study, there were no significant changes in liver or renal function after combination treatment with HMs and oral antihistamines. There were also no adverse event reports of pseudoaldosteronism or interstitial pneumonia.

We observed that the concurrent use of one or two antihistamines once or twice a day within 30 minutes of HM intake for a relatively short period of time improved clinical symptoms without liver and renal function changes through this retrospective chart review. No significant reductions in serum total IgE levels and eosinophil counts were observed in this study.

The present study has several limitations. First, the number of observed patients was relatively small. During hospitalization, we managed all treatment-related processes except those provided by the hospital, which is the advantage of inpatient care. However, this decreased the number of patients who met inclusion criteria for this study. Therefore, our study may have a low statistical power to observe the effectiveness of HMs with antihistamines for AD. Second, this is a retrospective chart review of AD patients who received HM with antihistamines and does not include a control group to compare the effectiveness and safety. In addition, due to the retrospective nature of this study, there may have been a selection bias that arises from the selection of a particular population. In addition, by observing only the recorded information, information bias may have occurred due to the limitation of the quality and quantity of medical records. Information bias may have affected safety assessments.

Because of these limitations, it is difficult to generalize the results of this study. Finally, the patients did not undergo a long-term treatment with HMs in combination with oral antihistamines. Patients who have chronic diseases such as AD tend to use HMs for a longer time period, and this may be associated with liver injury.

Despite these limitations, to the best of our knowledge, this is the first report regarding the effectiveness and safety of combination treatment with HMs and oral antihistamines for the treatment of AD, and our results may serve as the basis for further studies.

In summary, the results of our study suggest that the short-term combination treatment of AD with HMs and oral antihistamines is safe and effective, with a low risk of adverse reactions. Further prospective studies with long-term follow-up periods are necessary to further clarify our findings.

Conflicts of interest

The authors declare that they have no competing interests.

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REFERENCES

1. Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999;103:125–38.
2. Novak N. New insights into the mechanism and management of allergic diseases: atopic dermatitis. *Allergy* 2009;64:265–75.
3. Hong J, Buddenkotte J, Berger TG, Steinhoff M. Management of itch in atopic dermatitis. *Semin Cutan Med Surg* 2011;30:71–86.
4. Metz M, Stander S. Chronic pruritus-pathogenesis, clinical aspects and treatment. *J Eur Acad Dermatol Venereol* 2010;24:1249–60.
5. Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with non-sedating antihistamines: four prescription-event monitoring studies in general practice. *BMJ* 2000;320:1184–6.
6. Choi IH, Kim S, Kim Y, Yun Y. The effect of TJ-15 plus TJ-17 on atopic dermatitis: a pilot study based on the principle of pattern identification. *J Altern Complement Med* 2012;18:576–82.
7. Kim NK, Lee DH, Seo HS, Sun SH, Oh YL, Kim JE, et al. Hwangryunhaedoktang in adult patients with atopic dermatitis: a randomised, double-blind, placebo-controlled, two-centre trial?study. *BMC Complement Altern Med* 2011;11 http://dx.doi.org/10.1186/1472-6882-11-68.
8. Yun Y, Lee S, Kim S, Choi I. Inpatient treatment for severe atopic dermatitis in a Traditional Korean Medicine hospital: introduction and retrospective chart review. *Complement Ther Med* 2013;21:200–6.
9. Conn JW, Rovner DR, Cohen EL. Licorice-induced pseudoaldosteronism Hypertension, hypokalemia, aldosteronopenia, and suppressed plasma renin activity. *JAMA* 1968;205:492–6.
10. Ishizaki T, Sasaki F, Ameshima S, Shiozaki K, Takahashi H, Abe Y, et al. Pneumonitis during interferon and/or herbal

drug therapy in patients with chronic active hepatitis. *Eur Respir J* 1996;9:2691–6.
11. Lee WJ, Kim HW, Lee HY, Son CG. Systematic review on herb-induced liver injury in Korea. *Food Chem Toxicol* 2015;84:47–54.
12. Chak KF, Hsiao CY, Chen TY. A study of the effect of Shiunko, a traditional Chinese herbal medicine, on fibroblasts and its implication on wound healing processes. *Adv Wound Care (New Rochelle)* 2013;2:448–55.
13. Lu PJ, Yang C, Lin CN, Li CF, Chu CC, Wang JJ, et al. Shiunko and acetylshikonin promote reepithelialization, angiogenesis, and granulation tissue formation in wounded skin. *Am J Chin Med* 2008;36:115–23.
14. Lewis PA, Wright K, Webster A, Steer M, Rudd M, Doubrovsky A, et al. A randomized controlled pilot study comparing aqueous cream with a beeswax and herbal oil cream in the provision of relief from postburn pruritus. *J Burn Care Res* 2012;33:e195–200.
15. Cheng HM, Chiang LC, Jan YM, Chen GW, Li TC. The efficacy and safety of a Chinese herbal product (Xiao-Feng-San) for the treatment of refractory atopic dermatitis: a randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol* 2011;155:141–8.
16. Angelova-Fischer I, Neufang G, Jung K, Fischer TW, Zillikens D. A randomized, investigator-blinded efficacy assessment study of stand-alone emollient use in mild to moderately severe atopic dermatitis flares. *J Eur Acad Dermatol Venereol* 2014;28:9–15.
17. Klovekorn W, Tepe A, Danesch U. A randomized, double-blind, vehicle-controlled, half-side comparison with a herbal ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica for the treatment of mild-to-moderate atopic dermatitis. *Int J Clin Pharmacol Ther* 2007;45:583–91.
18. Schempp CM, Windeck T, Hezel S, Simon JC. Topical treatment of atopic dermatitis with St John's wort cream—a randomized, placebo controlled, double blind half-side comparison. *Phytomedicine* 2003;10:31–7.
19. Yun Y, Kim K, Choi I, Ko SG. Topical herbal application in the management of atopic dermatitis: a review of animal studies. *Mediators Inflamm* 2014 http://dx.doi.org/10.1155/2014/752103.
20. Simons FE, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol* 2011;128:1139–50.
21. Oh SJ, Cho JH, Son CG. Systematic review of the incidence of herbal drug-induced liver injury in Korea. *J Ethnopharmacol* 2015;159:253–6.
22. Park GJ, Mann SP, Ngu MC. Acute hepatitis induced by Shou-Wu-Pian, a herbal product derived from *Polygonum multiflorum*. *J Gastroenterol Hepatol* 2001;16:115–7.
23. World Health Organization. *WHO Monographs on Selected Medicinal Plants*. vol. 1. Geneva: World Health Organization; 1999.
24. Chen HY, Lin YH, Wu JC, Hu S, Yang SH, Chen JL, et al. Use of traditional Chinese medicine reduces exposure to corticosteroid among atopic dermatitis children: a 1-year follow-up cohort study. *J Ethnopharmacol* 2015;159:189–96.
25. Mizawa M, Makino T, Inami C, Shimizu T. Jumihaidokuto (Shi-Wei-Ba-Du-Tang), a kampo Formula, decreases the disease activity of palmoplantar pustulosis. *Dermatol Res Pract* 2016 http://dx.doi.org/10.1155/2016/4060673.
26. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab* 2015;66:8–16.
27. Ji HY, Chen XY, Jiao YZ, Tong XL. Analysis on dosage of traditional Chinese medicine decoction pieces stipulated in Chinese pharmacopoeia. *Zhongguo Zhong Yao Za Zhi* 2013;38:1095–7.
28. Willemsen MG, van Valburg RW, Dirven-Meijer PC, Oranje AP, van der Wouden JC, Moed H. Determining the severity of atopic dermatitis in children presenting in general practice: an easy and fast method. *Dermatol Res Pract* 2009 http://dx.doi.org/10.1155/2009/357046.
29. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. *Drugs* 2009;69:1777–98.