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The Effect of TJ-15 Plus TJ-17 on Atopic Dermatitis: A Pilot Study Based on the Principle of Pattern Identification

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Abstract

Aim: *Hwang-Yeon-Hae-Dok-San* (TJ-15) and *Ou-Ryung-San* (TJ-17) are two common herbal formulas that have been used to treat atopic dermatitis (AD), especially the Dampness-Heat pattern of AD. The aim of this study was to determine the safety and efficacy of TJ-15 plus TJ-17 for patients with the Dampness-Heat pattern of AD based on pattern identification.

Methods: This study was a parallel, randomized, active-controlled, double-blind trial. A total of 24 patients were enrolled. Either a combination of TJ-15 plus TJ-17, or TJ-15 alone was orally administered 3 times daily for 4 weeks. Of the patients enrolled, 19 patients completed the 4-week treatment course (TJ-15 plus TJ-17: $n=8$, TJ-15: $n=11$). Efficacy was assessed using the scoring atopic dermatitis (SCORAD) index; area of eczema and severity index (EASI); as well as the symptoms related to the Dampness-Heat by pattern identification. Efficacy measures were evaluated at the baseline and at 4 weeks. Safety was assessed throughout the study using ongoing laboratory tests.

Results: Both the SCORAD and EASI showed more improvement in the TJ-15 plus TJ-17 group than in the TJ-15 group; however, the differences were not statistically significant. The symptoms related to the Dampness-Heat pattern were reduced in both groups, and the changes were similar. There were no reported adverse events during this study, or abnormalities observed on aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine testing.

Conclusions: The results of this study suggest that both the TJ-15 plus TJ-17 and the TJ-15 provided safe and effective treatment for patients with the Dampness-Heat pattern type of AD.

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease, the incidence of which has been increasing over the past several decades.[1] As a result, AD has become a problem that affects people of all ages. In addition, the impact of AD on the overall quality of life, including financial burden, can be a significant issue for patients and their families.[2–4]

Over the past 20 years, there has been a significant increase in the use of complementary and alternative medicine—including herbal medicine—in patients with chronic inflammatory dermatoses, especially atopic dermatitis.[5,6] The increase in the use of herbal medicine is associated with both doctors' and patients' dissatisfaction with some aspects of the conventional treatment for AD,[7] especially now that a number of studies have demonstrated the safety and efficacy of herbal medicine for treating AD.[8–13] Most studies on herbal medicine for AD, however, have used fixed herbal formulae that have not considered one of the fundamental principles of herbal medicine, that being pattern identification (*bian zheng*). According to the World Health Organization, pattern identification is defined as the overall analysis of clinical data to determine the location, cause, and nature of a patient's disease and the diagnosis for any such given pattern.

In applying this principle to patients with AD, both *Dampness and Heat syndromes* diagnosed by pattern identification are considered the main pathogenic features of the acute stage of AD. Currently, there are some attempts to align Traditional Chinese Medicine (TCM) or Traditional Korean Medicine (TKM) research with clinical practice by using pattern identification.[14,15] However, there is no previous research on the treatment of patients with AD based on pattern identification. *Hwang-Yeon-Hae-Dok-San* (TJ-15, Tsumura Co. Ltd., Japan) is known to eliminate Heat toxicity from the interior,[16] and *Ou-Ryung-San* (TJ-17, Tsumura Co. Ltd., Japan) is known to control body fluids and help reduce the excess Dampness of the body.[17] When a certain symptom is identified by pattern identification, it

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is very important to treat patients with appropriate herbal drugs.

TJ-15, a traditional Chinese herbal compound, has been reported to be effective in treating noninfectious chronic inflammatory diseases. TJ-17 is a well-known blended traditional Chinese herbal medicine specifically used for the treatment of renal diseases characterized by edema, dysuria, and oliguria. It is hypothesized that the combination of TJ-15 plus TJ-17 is a better treatment than TJ-15 alone for Dampness-Heat pattern because it is more focused on treating Dampness-Heat pattern. Therefore, the changes in the SCORAD and EASI scores were assessed as well as changes in the nine symptoms of Dampness-Heat pattern as well. The aim of this pilot study was to determine the effects of TJ-15 plus TJ-17 on the Dampness-Heat pattern of patients with AD based on pattern identification.

Methods

Subjects

Prior to recruitment, this study was approved by the Institutional Review Board of the Kyung Hee University Hospital at Gangdong where this study was conducted. Informed consent was obtained from all of the patients. For patients under 18 years of age, an informed consent was obtained from their parents or guardians. Patients were recruited by a local advertisement and ads on hospital bulletin boards. Among those screened ($n=60$), all patients were diagnosed according to Hanifin and Rajka's criteria,[18] and were diagnosed with the Dampness-Heat pattern type of AD[9,13] according to pattern identification by a TKM dermatology specialist. Subjects with the following were excluded: patients taking antihistamines and/or steroids within 4-weeks prior to the study; patients with seizures; pregnant or lactating patients; and those with serious medical conditions, including infections. In addition, patients who initially met the inclusion criteria, but later showed abnormal results on the alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine testing were excluded. As a result, a total of 24 subjects were eligible and randomized for the study.

Study design

This study—a parallel, randomized, actively controlled, double-blind trial—was undertaken to assess the effects of TJ-15 plus TJ-17 compared to TJ-15 alone. In addition, the safety profiles of both TJ-15 plus TJ-17 and TJ-15 were examined.

Randomization

Randomization was performed using a computer-generated random numbers table. In order to maintain the randomization, the random numbers table and the intervention allocations were made known after analyzing the data.

Blinding

After the eligible subjects were enrolled, a pharmacist randomly assigned subjects to either the TJ-15 plus TJ-17 group, or the TJ-15 group according to the randomization table. All participants were given the same dose of TJ-15 plus TJ-17, or TJ-15 in an identical package. All subjects were given instructions from the pharmacist independently as to which herbal extracts they were going to take to treat the AD.

Table 1. Crude Drug Composition of TJ-15

Scientific name	*Used part*	*Composition (g)*
Scutellaria baicalensis	Root	3.0
Gardenia jasminoides	Fruit	2.0
Coptis chinensis	Rhizome	2.0
Phellodendron amurense	Bark	1.5

A TKM doctor assessed the subjects during the study, and an independent statistician analyzed the data.

Pattern identification

Criteria for the diagnosis of the Damp-Heat pattern were used according to the principles of TCM/TKM; at least four of the following nine symptoms were required: (1) rapid change in signs and conditions, (2) excessive itching, (3) vesicles, (4) oozing, (5) discomfort during defecation, (6) gastric bloating and distention, (7) red-brownish urine and discomfort when urinating, (8) thickly coated and slippery red tongue, and (9) rapid pulse. When a symptom was present it was coded as 1, and when no symptom was present it was coded as 0. In this way, the total number of symptoms was tallied.

Background information and control of extraneous factors

The background information collected included the following: gender, age, onset of AD, state of the lesions, family history, and past history of allergic disease. Specific instructions on diet were suggested, as well as potential environmental triggers and moisturizing methods for patient symptom management. In general, most patients and their families thought that their signs and symptoms were related to diet and environmental exposures, including specific allergens. Most asked about methods to better manage their daily life, including diet and environmental factors, to help alleviate the symptoms. In addition to treatment, certain dietary and environmental recommendations were made to all participants.

Herbal formulas, preparation, and administration for TJ-15 and TJ-17

The components of TJ-15 and TJ-17 are described in Tables 1 and 2. The doses were adjusted depending on the subject's weight (Table 3). Briefly, for the TJ-15 plus TJ-17 group, 1.25 g of TJ-15 (Tsumura Co. Ltd., Japan) and 1.25 g of TJ-17 (Tsumura Co. Ltd., Japan) were mixed and ingested 90 minutes after a meal, 3 times a day, for a total of 7.5 g per day. For the TJ-15 alone group, 2.5 g of TJ-15 (Tsumura Co. Ltd., Japan) was ingested 90 minutes after a meal, 3 times a

Table 2. Crude Drug Composition of TJ-17

Scientific name	*Used part*	*Composition (g)*
Alisma orientalis	Root tuber	4.0
Poria cocos	Mycelium	3.0
Atractylodes lancea	Rhizome	3.0
Cinnamomum cassia	Branch	1.5
Polyporus umbellatus	Mycelium	1.5

Table 3. Dose Depending on Patients' Weight

Patients' weight (kg)	*Total dose (g)*
Over 50	2.5
20–50	1.6
Less than 20	0.8

day, for a total of 7.5 g per day. Both groups were clinically examined at the beginning of the study, and at 1 week, 2 weeks, and 4 weeks; all participants received treatments for 4 weeks, until the end of the study.

Concomitant medications

Different combinations of medicine were allowed, but patients taking antihistamines, steroids, and immunesuppressant treatment were excluded. After discussion with the investigators, patients who used emollients, lotions, and ointments that do not contain steroids were included. Patients were only allowed to use emollients, lotions, and ointments that do not contain steroids during the study.

Efficacy

Efficacy outcomes were evaluated using three instruments: SCORAD, EASI, and the various symptoms measured by Pattern identification/Symptom differentiation. The results of the SCORAD, "SCORing Atopic Dermatitis," were the primary endpoint, whereas for the results of the EASI, "Eczema Area and Severity Index," symptoms examined for pattern identification were the secondary endpoints. The clinical manifestations of symptoms including erythema, edema/papule, oozing/crust, excoriation, lichenification, and dryness were also recorded as secondary endpoints. The severity of these symptoms were grouped into four categories: severe (3), moderate (2), mild (1), and absent (0).

Safety

Patients with adverse events during the study, including nausea, vomiting, stomach discomfort, fever, and/or diarrhea, were monitored closely by clinicians. The safety associated with treatment was also assessed by laboratory tests including AST, ALT, BUN, and creatinine at the first and final visits. In addition, physical examinations were performed at the beginning of the study, at 1 week, 2 weeks, and 4 weeks after the start of treatment.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) or n (%). Due to the small sample size of this pilot study, statistical data analysis was performed using nonparametric tests including the Wilcoxon rank sum test and the Fisher's exact test (SAS version 9.1; SAS Institute, NC). A p-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Among the 60 Korean participants screened, 24 were eligible for this study. A total of 24 patients were randomly assigned to receive either TJ-15 plus TJ-17 ($n = 12$) or TJ-15 alone ($n = 12$). There was no difference between the two groups in terms of the baseline characteristics. The baseline disease severity was also similar between the two groups (Table 4). A total of 8 patients (66.7%) in the TJ-15 plus TJ-17 group, and 11 (91.7%) patients in the TJ-15 group completed the study. Four (33.3%) patients in the TJ-15 plus TJ-17 group were dropped because of unsatisfactory therapeutic effects reported by the patients themselves ($n = 2$), protocol violation (topical steroids use) ($n = 1$), and loss to follow-up ($n = 1$). One (8.3%) patient in the TJ-15 group was excluded because of loss to follow up (Fig. 1).

Table 4. Baseline Demographics and Clinical Characteristics

Characteristics	*No. (%) or mean ± SD*		p-*Value*
	TJ-15 plus TJ-17	*TJ-15*	
Age	18.6 ± 8.4	14.2 ± 6.0	0.27[a]
5≤ age <18	6 (50.0%)	7 (58.3%)	
18≤ age ≤32	6 (50.0%)	5 (41.7%)	
Sex			1[b]
Male	5 (41.7%)	5 (41.7%)	
Female	7 (58.3%)	7 (58.3%)	
Duration of atopic dermatitis (yrs)	14.7 ± 8.8	10.4 ± 5.9	0.14[a]
Western treatment experience (yes)	12 (100.0%)	9 (75.0%)	0.22[b]
Oriental treatment experience (yes)	8 (80.0%)	7 (58.3%)	0.38[b]
Past history	9 (75.0%)	6 (50.0%)	0.40[b]
Allergic rhinitis	5 (41.7%)	9 (75.0%)	0.21[b]
Allergic asthma	0 (0.0%)	2 (16.7%)	0.48[b]
Allergic conjunctivitis	0 (0.0%)	2 (16.7%)	0.48[b]
Food allergy	10 (83.3%)	10 (83.3%)	1[b]
Family history	8 (66.7%)	5 (41.7%)	0.41[a]
EASI score	23.8 ± 19.7	21.4 ± 13.7	0.89[a]
SCORAD	56.1 ± 6.9	50.9 ± 10.3	0.27[a]
Serum total IgE			1[b]
Normal	10 (83.3%)	11 (91.7%)	
Abnormal	2 (16.7%)	1 (8.3%)	
Eosinophil count			1[b]
Normal	9 (75.0%)	10 (83.3%)	
Abnormal	3 (25.0%)	2 (16.7%)	

[a]Wilcoxon rank sum test.
[b]Fisher's exact test.
SD, standard deviation; EASI, eczema and severity index; SCORAD, scoring atopic dermatitis index; IgE, immunoglobulin E.

Efficacy

The SCORAD index. The primary efficacy measure was the severity of the AD assessed by the SCORAD index. The mean modified SCORAD after 4 weeks from baseline was −27.2 ± 8.9 in the TJ-15 plus TJ-17 group and −24.9 ± 13.7 in TJ-15 group. The degree of reduction in the SCORAD found in the TJ-15 plus TJ-17 group was greater than in the TJ-15 group; however, the difference was not statistically significant (Table 5).

EASI score. The mean EASI score after 4 weeks of treatment was −16.9 ± 12.1 in the TJ-15 plus TJ-17 group and −10.4 ± 7.9 in the TJ-15 group. The reduction found in the TJ-

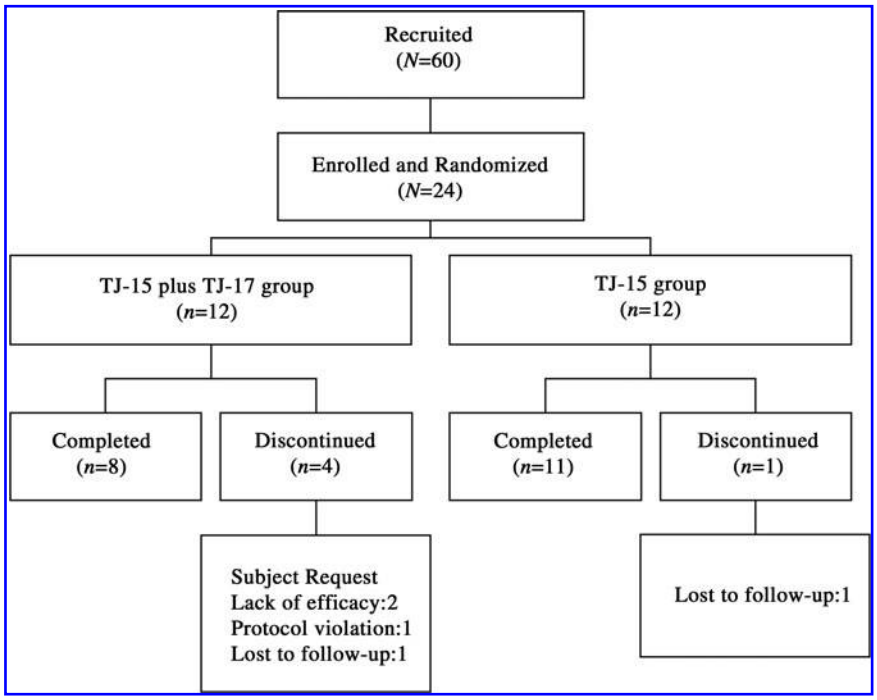


FIG. 1. Patient flow chart.

15 plus TJ-17 group was greater than in the TJ-15 group; however, the difference was not statistically significant (Table 6).

Pattern identification. Of nine symptoms of the Damp-Heat pattern: (1) rapid change in the signs and conditions; (2) excessive itching; (3) vesicles; (4) oozing; (5) gastric bloating and distention; (6) discomfort during defecation; (7) red–brownish urine, discomfort when urinating; (8) thickly coated and slippery red tongue; and (9) rapid pulse, the mean (and SD) number of symptoms at baseline and after 4 weeks of treatment are presented in Table 7.

In addition, the mean (SD) number of symptoms improved/deteriorated from baseline to 4 weeks after treatment (Table 7). Briefly, the mean (SD) number of symptoms at baseline was 5.4 (1.6) for the TJ-15 only group and 5.4 (1.2) for the TJ-15 plus TJ-17 group.

There was no difference between the two treatment groups at baseline in terms of the number of symptoms. The mean (SD) number of symptoms after 4 weeks of treatment was 2.5 (1.3) for the TJ-15 only group and 3.4 (1.4) for TJ-15 plus TJ-17 group. Both treatment groups improved; however, there was no significant difference between the two groups. The mean (SD) number of reduced symptoms was 2.4 (1.3) and 2.1 (1.6) for TJ-15 only and the TJ-15 plus TJ-17 group, respectively (Table 7).

Safety

There were no reported cases with adverse events or abnormalities of the AST, ALT, BUN, and creatinine levels during and after the 4 weeks of treatment in either group.

Discussion

This is the first study using herbal extracts on atopic dermatitis based on the principle of pattern identification. Pattern identification is a unique diagnostic system entailing comprehensive analysis of symptoms and signs with implications for determining the cause, nature, and location of the illness, the patient's physical condition, and the patient's treatment.[15] TCM/TKM doctors differentiate symptoms into patterns of disease, and then treat the patients based on pattern identification.

Despite its central role, pattern identification has not been well integrated into clinical research; therefore, it is very difficult to preserve the concept of pattern identification while maintaining a rigorous study design. Recently, TCM/TKM research methodology and concept have progressed

Table 5. Change of SCORAD Score

Group	*Week 0*	*Week 4*	*Difference between weeks 0 and 4*	p-*Value*[a]
TJ-15 plus TJ-17	56.1 ± 6.9 (12)	28.7 ± 10.1 (8)	−27.2 ± 8.9	0.0078
TJ-15	50.9 ± 10.3 (12)	25.0 ± 11.0 (11)	−24.9 ± 13.7	0.0010
p-Value[b]	0.2700	0.5400	0.6600	

Data are mean ± standard deviation (*n*).
[a]Paired *t*-test.
[b]Wilcoxon rank sum test.
SCORAD, scoring atopic dermatitis index.

Table 6. Change of EASI Score

Group	*Week 0*	*Week 4*	*Difference between weeks 0 and 4*	p-*Value*[a]
TJ-15 plus TJ-17	23.8±19.7 (12)	10.4±11.8 (8)	−16.9±12.1	0.0078
TJ-15	21.4±13.7 (12)	9.7±9.8 (11)	−10.4±7.9	0.0010
p-Value[b]	0.8900	0.7800	0.2100	

Data are mean±standard deviation (*n*).
[a]Paired *t*-test.
[b]Wilcoxon rank sum test.
EASI, eczema and severity index.

slightly concerning pattern identification.[14,15,19,20] However, most studies of AD using herbal medicine still use fixed herbal formulas, which means that they have not considered pattern identification.

The aim of this study was to determine the safety and efficacy of TJ-15 plus TJ-17 compared to TJ-15 only for patients with the Dampness-Heat pattern type of AD based on pattern identification.

For studying the efficacy and safety of TJ-15 plus TJ-17 for patients with the Dampness-Heat pattern type of AD, only AD patients of the Dampness-Heat pattern type were recruited. Also, we observed nine categories of Dampness-Heat symptoms to determine changes in the Dampness/Heat pattern.

There were no adverse events reported including nausea, vomiting, stomach discomfort, fever, and diarrhea, as well as no abnormalities of the AST, ALT, BUN, and creatinine levels in either treatment group during and after the trial. Both the SCORAD index and EASI score decreased in both groups compared to baseline, and decreased more in the TJ-15 plus TJ-17 group when compared to the TJ-15-only group; however, the treatment differences were not statistically significant. When the nine categories of symptoms that determine changes in the Dampness/Heat pattern were considered over the 4-week trial, the Dampness-related symptoms seemed to be better resolved in the TJ-15 plus TJ-17 group, while the heat-related symptoms tended to resolve in the TJ-15 group; however, the differences were not statistically significant.

For the conventional medical treatment of AD, the first step usually involves the use of topical steroids, topical tacrolimus, emollients, and oral antihistamines, and for the second step, systematic steroids and immunosuppressants are used. However, these medications can have adverse effects. For this reason, most patients would like to avoid the risks associated with these medical agents if possible.[21] Therefore, most patients with AD and their families who visit TCM/TKM clinics and hospitals are looking for safer herbal medicine treatments that can provide therapeutic effects, without recurrence of symptoms or long-term harmful consequences.

Table 7. Basic Characteristics of the Patients by SCORAD

Intensity score	*0*	*1*	*2*	*3*
Erythema			9 (37.5%)	15 (62.5%)
Edema/papule		5 (20.8%)	13 (54.2%)	6 (25.0%)
Oozing/crust	1 (4.2%)	4 (16.7%)	15 (62.5%)	4 (16.7%)
Excoriation		4 (16.7%)	15 (62.5%)	5 (20.8%)
Lichenification		1 (4.2%)	7 (29.2%)	16 (66.7%)
Dryness			4 (16.7%)	20 (83.3%)

SCORAD, scoring atopic dermatitis index.

Certain herbs and herbal formulas are commonly used to treat eczematous conditions. In 2005, the efficacy of these treatments was assessed by a Cochrane Collaboration review,[22] including four randomized controlled trials (RCTs) up to the year 2004.[9,13,23,24] According to the review, herbal mixtures may be effective for the treatment of AD. However, four small, poorly reported RCTs using the same product, Zemaphyte, were found to be inconclusive.[23] In addition, the side-effects associated with Zemaphyte raised concerns about potential hepatic and renal toxicity.[25]

For methodological reasons, all of the previous studies mentioned previously have used the same herbal formula for all patients. However, a recently published double-blind controlled study assessing the efficacy of an ancestral formula containing five herbs for the treatment of AD, for 12 weeks of treatment, showed a 14.7% reduction in the clinical scores.[10] However, the identification of the patients was not consistent with the principles of TCM/TKM philosophy, and this might have affected the efficacy. Another multicenter, double-blind, randomized, placebo-controlled study reported on the safety and efficacy of a traditional herbal medicine, *Hochu-ekki-to* on *Kikyo* (or delicate constitution) in patients with AD. The study results demonstrated that *Hochu-ekki-to* significantly reduced the required dose of topical steroids and/or tacrolimus without further aggravating the underlying condition.[26]

Due to the contradictory results of previous studies and the limited number of trials assessing the effects of herbal medicine in patients with AD, this study of TJ-15 plus TJ-17 was carried out based on pattern identification, a basic principle of TCM/TKM. *Huanglian Jiedu san* or TJ-15, an herbal compound, has been reported to be effective in treating noninfectious chronic inflammatory diseases including cerebral and cardiovascular diseases. In general, TJ-15 has been used for draining Fire, expelling toxins, and clearing Damp-Heat.[16] *Wulingsan*, TJ-17, is a well-known blended herbal compound specifically used for the treatment of renal diseases characterized by edema, dysuria, and oliguria. TJ-17 has been widely used for promoting urination, draining Dampness, strengthening the Spleen, warming the *Yang*, and promoting the transforming function of the bladder.[15]

The combination of TJ-15 and TJ-17 has been considered to be more effective than TJ-15 alone in patients with the Dampness-Heat pattern of AD, because it works not only on heat, but also on Dampness pathogens. Using this principle of pattern identification, a randomized controlled study comparing TJ-15 plus TJ-17 treatment to TJ-15 treatment was carried out.

This study has several limitations. There were no statistically significant differences between the two groups.

However, it is possible that a Type II error may have occurred because there was a small number of participants in each study group; there was also no follow-up after the treatment period. The long-term effects of any intervention for AD are important; this is because AD is a chronic disorder with relapse and remission cycles influenced by many factors. In addition, there is no standard treatment for AD based on evidence-based medicine that could be used for comparison. Therefore, it is very difficult to rate an intervention compared to a standard herbal medicine. Furthermore, there is an issue of inter-rater reliability of pattern diagnosis. To the authors' the present knowledge, there is no validated and standardized pattern-diagnosing system for AD, so a numeric rating system was used in this present study.

Developing reliable and valid outcome measurement within TCM/TKM concepts and frameworks are essential for evaluating TCM treatment. Biomedical testing may not relate to the patients' quality of life or the presence and severity of symptoms and therefore may not be the best method to evaluate TCM/TKM disciplines that primarily focus on patients' health, patterns, and symptom clusters.[14] In this present study, Dampness-Heat-pattern-related symptom scores were used as an outcome measurement.

While there were a number of limitations in this study, the authors believe that this approach using pattern identification as a diagnostic and a measurement instrument is a worthy strategy for applying RCT and evidence-based medicine standards to TCM/TKM treatment on AD. In the future, more research using modified and improved research methods is needed to evaluate TCM/TKM treatment for AD.

Conclusions

In conclusion, the TJ-15 plus TJ-17 group showed similar outcomes when compared with the TJ-15-only group in patients with the Dampness-Heat pattern of AD; there were no significant differences between these two study groups. Both groups of patients showed some improvement in their signs and symptoms without any adverse events. After a trial period of 4 weeks, the SCORAD and EASI results showed a significant decrease from the baseline in both treatment groups (p's=0.0078 and 0.0010), but not between the two treatment groups. Therefore, it may be concluded that without a non-medication control, both combination therapy (TJ-15 plus TJ-17) and single therapy (TJ-15) resulted in a decline in severity of AD for patients with the Dampness-Heat pattern of AD.

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Disclosure Statement

No financial conflicts exist.

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