

A Pentaherbs Capsule as a Treatment Option for Atopic Dermatitis in Children: An Open-Labeled Case Series

Kam-Lun Ellis Hon, Ting-Fan Leung, Yin Wong, Wai-Kei Christopher Lam,* De-Qi Bill Guan,[†]
Kwok-Chiu Ma, Yn-Tz Rita Sung, Tai-Fai Fok and Ping-Chung Leung[†]
*Departments of Paediatrics and *Chemical Pathology, and [†]Institute of Chinese Medicine
The Chinese University of Hong Kong, Prince of Wales Hospital
Shatin, Hong Kong SAR, China*

Abstract: Traditional Chinese Medicine (TCM) has been used in patients with atopic dermatitis (AD), but its therapeutic effects are debatable. We evaluated the clinical and biochemical effects of a TCM capsule (PentaHerbs capsule) in children with AD. After a run-in period of 4 weeks, children old enough to manage oral medication were admitted and their disease severity was evaluated by the SCORing Atopic Dermatitis (SCORAD) index. Blood was obtained for complete blood count, total and allergen-specific immunoglobulin E (IgE), biochemical studies and inflammatory markers of AD severity [serum cutaneous T cell-attracting chemokine (CTACK), macrophage-derived chemokine (MDC), thymus and activation-regulated chemokine (TARC) and eosinophil cationic protein (ECP)] prior to, and after 3 months of, TCM use. Three PentaHerbs capsules twice a day were prescribed for 4 months. Patients were followed monthly to ensure compliance, and SCORAD scores were obtained at each visit. Five boys and four girls participated in the study. All patients had detectable food or inhalant-specific IgE in serum. There was significant improvement in the overall and component SCORAD scores. There were no significant differences between the pre- and post-treatment values of the serum CTACK, MDC, TARC and ECP levels but CTACK showed a decreasing trend ($p = 0.069$). No clinical or biochemical evidence of any adverse drug reaction was observed during the study period. The PentaHerbs capsules were well tolerated by the children and apparent beneficial effects were noted clinically. A larger, randomized placebo-controlled study is required to confirm the efficacy of this formulation for AD.

Keywords: Traditional Chinese Medicine; Atopic Dermatitis; Children.

Introduction

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease commonly associated with inhalant allergy (Leung, 1995). AD typically presents in early childhood with onset before five years of age in about 90% of patients. Fifteen percent of schoolchildren aged 13 to 14 years have had a past history of AD (Leung *et al.*, 1997). Corticosteroids (CS), either in topical or systemic formulations, are the mainstay of treatment. CS have a wide range of immunomodulatory effects including the suppression of cytokine production, adhesion molecule expression and leukocyte chemotaxis (Pucci *et al.*, 2000). CS are also associated with deranged metabolism, growth suppression and increased susceptibility to infection. Potent topical CS can result in significant suppression of the hypothalamic-pituitary-adrenal axis (Ellison *et al.*, 2000). Despite the use of CS and newer and more specific immunomodulatory agents, some patients remain symptomatic and may seek complementary medicine in the form of Chinese herbs. Although traditional Chinese medicine (TCM) is widely used in many Asian societies, its beneficial effects on children with AD have not been consistently demonstrated and undesirable side effects have been noted. Our pilot study aimed to (1) evaluate the clinical effects of TCM by SCORAD score, (2) compare the levels of serum immune markers before and after PentaHerbs use for children with AD, and (3) document adverse effects of PentaHerbs on hematologic, hepatic and renal functions.

Methods

Subjects

Children with AD diagnosed according to Hanifin (Hanifin and Rajka, 1980) criteria were recruited from the pediatric dermatology outpatient clinic of a university teaching hospital. The SCORing atopic dermatitis (SCORAD) index (Stalder *et al.*, 1993) was used to evaluate the clinical severity of AD. All subjects with a SCORAD score of ≥ 15 were eligible for inclusion into the study. Subjects were excluded if they had active concurrent disease other than allergic diseases such as asthma and allergic rhinitis, and if they received psoralen ultraviolet A (UVA) treatment within the previous 8 weeks. Informed written consent was obtained from the parents. Ethical approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

Study Design

Participants underwent a 4-week run-in period. During which time, their baseline dietary intake, emollient and drug use, and information of severity of AD were collected. They then received three PentaHerbs capsules (250 mg active herbs each) twice daily for 16 weeks. Physicians at our Institute of Chinese Medicine considered this dosage would suit a wide range of age groups. The principal investigator (Hon) explained the correct use of the medications to each subject and ensured that the subject was compliant to the treatment

regimen and using the medications properly. Enrolled subjects were followed up once every 4 weeks. Each patient was given an Eczema Diary for recording daily symptoms. The severity of AD was assessed (by Hon) with the SCORAD index (Stalder *et al.*, 1993). This was used as the primary outcome and was measured before, monthly, and at the end of the treatment period. The individual components of the SCORAD index (disease extent, intensity, pruritus and sleep loss), and the serum concentrations of serum cutaneous T cell-attracting chemokine (CTACK), macrophage-derived chemokine (MDC), thymus and activation-regulated chemokine (TARC) and eosinophil cationic protein (ECP) were the secondary outcome measures. Neither the potency of topical CS nor the type of oral anti-histamines used by individual subjects were changed during the study. Adherence to the study regimen was evaluated by comparing the number of capsules returned with the number recorded as taken in the Eczema Diary.

Laboratory Assays

Blood was obtained for complete blood count, total and allergen-specific immunoglobulin E (IgE), biochemical studies and inflammatory markers of AD severity before and at the end of the third month of PentaHerbs use. Serum samples were stored at -70°C until analysis. Serum concentration of total IgE was measured by micro-particle immunoassay (IMx analyzer, Abbott Laboratories, Abbott Park, IL, USA). Specific IgE to food allergens (cow's milk, egg white, wheat, soybean, fish, peanut, shrimp and orange) and prevalent inhalant allergens (*Dermatophagoides pteronyssinus* and mixed cockroaches) were measured by fluorescent enzyme immunoassay (AutoCAP system, Pharmacia Diagnostics AB, Uppsala, Sweden). Levels $\geq 0.35 \text{ k}_\text{A}\text{U/l}$ were classified as positive. Serum concentrations of CTACK, MDC and TARC were measured in duplicates by sandwich enzyme immunoassay (R&D Systems, Minneapolis, MN, USA). The lower limits of detection for these chemokines were 1.6, 62.5 and 7.0 pg/ml, respectively. Serum ECP concentration was measured by fluorescent enzyme immunoassay (AutoCAP system, Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden), with the detection limit of 0.5 $\mu\text{g/l}$.

PentaHerbs Capsule

The capsule was manufactured, packaged and labeled by the Chinese Medicine Industry Development Center, the Hong Kong Institute of Vocation Education, using Good Manufacturing Practice (GMP) standard. The optimal composition of each herb included was standardized prior to manufacturing. The powder was formulated into uniform dose capsules under the supervision of the Clinical Trials Section, Institute of Chinese Medicine of the Chinese University of Hong Kong according to established procedures. The original formula was: Flos Lonicerae (Jinyinhua) 2 g, Herba Menthae (Bohe) 1 g, Cortex Moutan (Danpi) 2 g, Rhizoma Atractylodis (Cangzhu) 2 g and Cortex Phellodendri (Huangbai) 2 g (total 9 g of raw herbs daily). The extraction rate from this raw herb was around 18%–20%, which made six to seven capsules. The dose calculation was based on the assumption that

patients had to be old enough to swallow the capsules without difficulty (between seven to 12 years of age). Before the clinical trial, the capsules were assessed by the Institute of Chinese Medicine for the presence of heavy metals, microbial products and residual pesticides to ensure that these met quality and safety requirements.

Statistics

Data were expressed as medians with ranges. Results on SCORAD and laboratory parameters in paired samples before and after PentaHerbs use were compared using the Wilcoxon signed ranks test. The correlations between SCORAD and inflammatory markers were analyzed by Spearman correlation coefficients. All comparisons were two-tailed, and *p* values less than 0.05 were considered significant.

Results

The study was conducted during the period January 2003 through August 2003. Nine Chinese children (five boys and four girls), with a median (range) age of 11.3 (5.0–13.5) years, were enrolled. Eight patients had good compliance with the prescribed PentaHerbs capsules, with one boy only taking about 75% of total dose of medication. One girl refused blood taking and dropped out at the end of the third month. All patients were sensitized to at least one food or inhalant allergens (Table 1).

At the end of the third month of treatment, seven of nine patients had a significant reduction in their overall SCORAD score (Fig. 1). The median (range) overall SCORAD score before and at the end of three months was 60.3 (20.0–82.6) and 40.0 (11.4–56.5), respectively (*p* = 0.008). Significant differences were also noted in the components of the SCORAD index (extent, intensity, pruritus and sleep loss) (Figs. 2a to 2d). The SCORAD initially improved in one boy (35.0 at the end of the first month and 42.0 at the end of second month) when compared to baseline (57.3). Towards the end of the third month, however, his eczema flared up in the lower limbs. *Staphylococcus aureus* was isolated in the skin swabs and he was treated with a course of oral antibiotic. The SCORAD, CTACK and MDC levels were all raised.

Significant correlations between baseline SCORAD, its components and serum inflammatory markers were noted (Table 2). We also observed a trend towards a reduction in serum CTACK concentration from 1663 (876–4066) pg/ml to 1383 (855–1985) pg/ml (*p* = 0.069). The median (range) serum MDC levels before and at the end of three months were 3159 (1665–7597) pg/ml and 1925 (927–4962) pg/ml (*p* = 0.161), whereas the corresponding results for TARC were 1482 (564–7005) pg/ml and 1130 (456–6105) pg/ml (*p* = 0.208). The median (range) serum ECP levels before and after medication were 37.4 (5.6–67.3) µg/l and 19.3 (10.9–28.8) µg/l, respectively (*p* = 0.123). Serum total IgE levels did not differ before and after medication (*p* = 1.000). None of the patients or their parents reported any adverse effects. There was no increase in the baseline oral anti-histamine or topical CS use during the study period. Hematological and biochemical profiles remained

Table 1. The Pattern of IgE Sensitization to Food and Inhalant Allergens in the Nine Subjects*

Allergens	Number (%) Positive [†]
Food allergens	
Cow's milk	3 (33)
Egg white	3 (33)
Wheat	5 (56)
Soybean	5 (56)
Fish	3 (33)
Peanut	5 (56)
Shrimp	6 (67)
Orange	3 (33)
Inhalants	
<i>D. pteronyssinus</i>	9 (100)
Cockroach	6 (67)

*Their median (range) serum total IgE level was 1117 (453–10493) kIU/l.

[†]Positivity defined as IgE levels ≥ 0.35 k_AU/l.

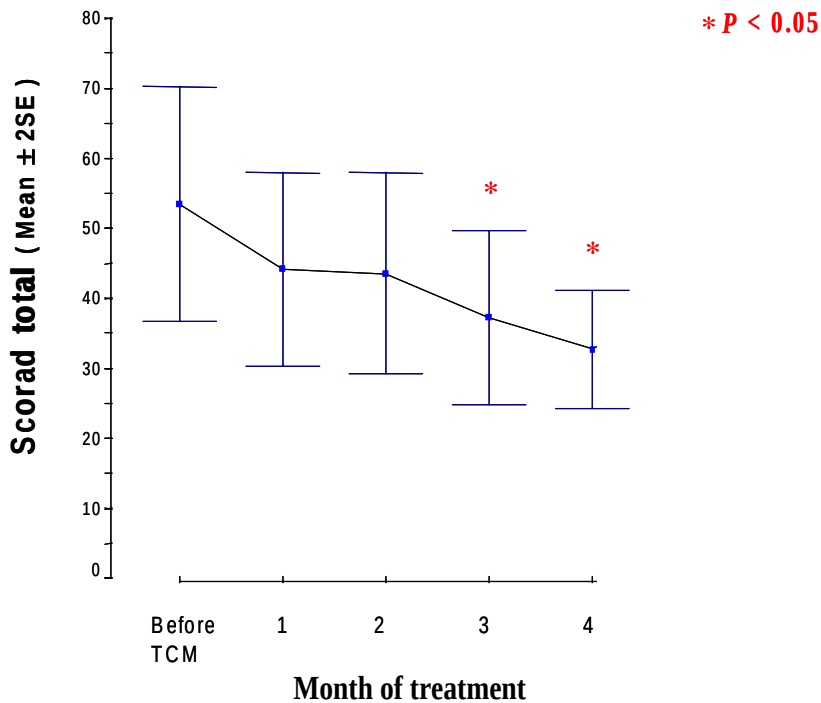


Figure 1. Serial changes of total SCORAD score in nine patients (eight for fourth month due to withdrawal).

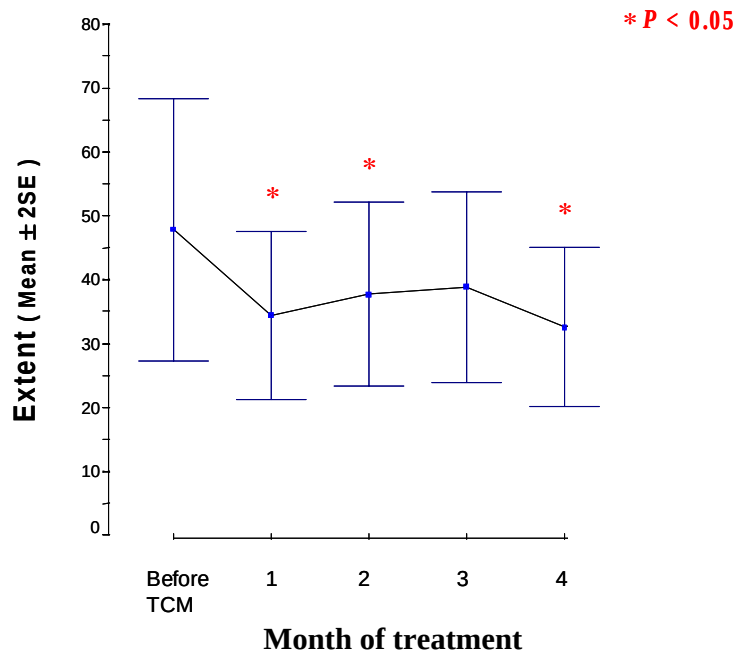


Figure 2a. Change in extent of disease during the study period.

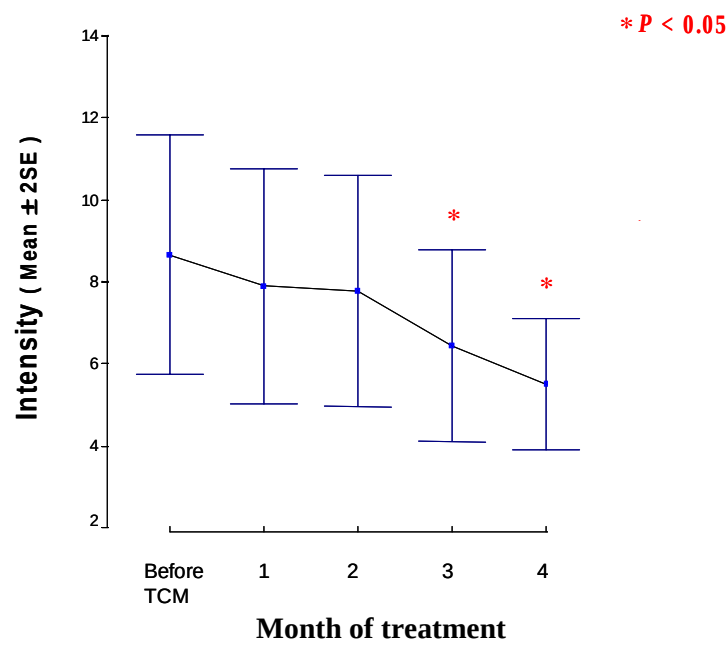


Figure 2b. Change in disease intensity during the study period.

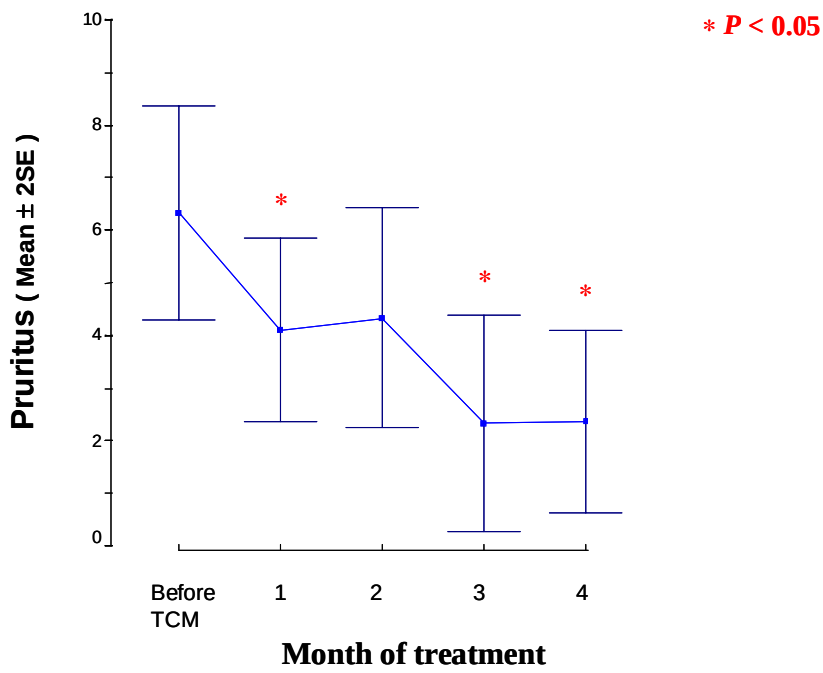


Figure 2c. Change in subjective symptom of pruritus during the study period.

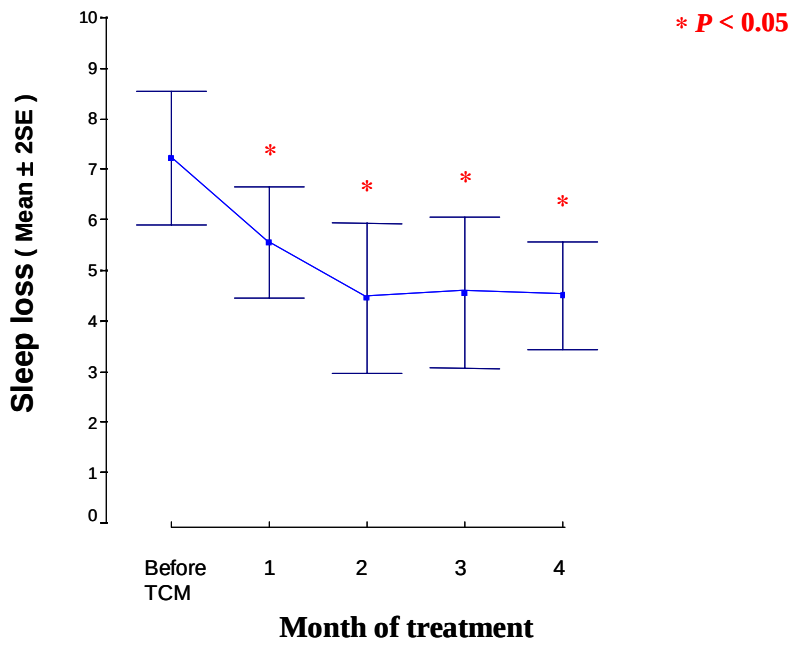


Figure 2d. Change in subjective symptom of sleep loss during the study period.

Table 2. Correlations Between SCORAD Score and Serum Inflammatory Markers at Baseline

	CTACK		MDC		TARC		ECP	
	r	p	r	p	r	p	r	p
Total SCORAD	0.917	0.001	0.867	0.002	0.750	0.020	0.467	0.205
SCORAD components								
Extent	0.950	<0.001	0.900	0.001	0.733	0.025	0.450	0.224
Intensity	0.937	<0.001	0.810	0.008	0.836	0.005	0.354	0.349
Subjective symptoms	0.770	0.015	0.870	0.002	0.494	0.177	0.544	0.130
Sleep loss	0.728	0.026	0.879	0.002	0.485	0.185	0.611	0.081
Pruritus	0.798	0.010	0.824	0.006	0.555	0.121	0.454	0.220

within normal limits during the treatment phase in the eight patients who completed the study.

Discussion

In this small case series, we showed that PentaHerbs capsules significantly improved AD disease severity and the distressing symptoms of itch and sleep loss. The therapeutic effects appeared to persist for one month after treatment had stopped. In Chinese medicine, “wind”, “dampness” and “heat” are considered to be the main pathogenic factors. The five herbs used in the study of this formulation are proposed to work as follow: *Jingyinhua* and *Bohe* clear wind-heat from the exterior, *Danpi* clears heat from blood, while *Cangzhu* and *Huangbai* clear the wind-heat from interior. These herbs have been extensively used in China for treatment of allergic diseases including eczema, asthma and allergic rhinitis. Pharmacological studies have documented that these herbs have anti-allergic, anti-inflammatory and sedative action for itch and they have been previously used in the study of childhood AD (Huang, 1998; Xu *et al.*, 1997).

Some herbs such as *Cortex Moutan Radix*, *Radix Paeoniae Alba*, *Potentilla Chinensis* Ser and *Radix Glycyrrhizae* are also commonly used in eczematous conditions (Zhang, 1990). The earlier studies noted that *Clematis armandii*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrestris* and *Schizonepeta tenuifolia* had been shown to be beneficial and safe for the treatment of severe AD in both children (Sheehan and Atherton, 1994) and adults (Sheehan *et al.*, 1995). However, adverse effects of Chinese herbal medicines have also been reported (Atherton *et al.*, 1992; Ferguson *et al.*, 1997; Fung *et al.*, 1999; Graham-Brown, 1992; Graham-Brown *et al.*, 1994; Perharic-Walton and Murray, 1992; Perharic *et al.*, 1995). This concern is heightened by the fact that TCM is not standardized and varies with the prescriptions of individual practitioners. It is believed that standardization of herbal mixtures is in contradiction to Chinese medical philosophy (Atherton *et al.*, 1992).

In Hong Kong, a controlled trial of Zemaphyte (a standardized formulation containing ten Chinese herbs) was conducted on 37 Chinese patients with recalcitrant AD for 8 weeks. No beneficial or adverse biochemical effects were demonstrated (Fung *et al.*, 1999). None of these herbs have pharmacological evidence regarding anti-allergic and anti-inflammatory effects. *Clematis armandi* used in Sheehan and Atherton's studies has diuretic effect and its long-term use necessitates potassium supplementation to avoid hypokalemia. This herb was not used in our study in view of this safety concern.

CTACK has been shown to be a skin-specific chemokine that correlates with AD severity both in adults (Barton *et al.*, 1994; Phillips *et al.*, 1987) and in children (Hon *et al.*, 2004). A no significant trend to improvement in serum CTACK levels was noted. Excluding the boy with skin exacerbation due to *Staphylococcus aureus* infection, the reduction in CTACK levels in the remaining patients then became significant ($p = 0.018$). This result suggests that our PentaHerbs formulation may have some degree of anti-inflammatory effect for AD.

This pilot study was limited by the small sample size, because of the unexpected Severe Acute Respiratory Syndrome (SARS) outbreak in Hong Kong. We had to stop the recruitment to avoid patients entering the hospital premises. Despite this limitation, the clinical effects of the PentaHerbs capsules for AD appear impressive and deserve further evaluations in a randomized controlled trial.

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