Clinical and Experimental Dermatology and Therapies
LEUNG P. C., et al. Clin Exp Dermatol Ther 7: 173.
www.doi.org/10.29011/2575-8268.100173
www.gavinpublishers.com

Commentary

Development of Supplementary Treatment Programs for the Control of Atopic Dermatitis

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Citation: LEUNG Ping-Chung, CHENG King-fai William, Kam Lun Ellis Hon (2022) Development of Supplementary Treatment Programs for the Control of Atopic Dermatitis. Clin Exp Dermatol Ther 7: 173 DOI: 10.29011/2575-8268.100173

Received Date: 06 January 2022; **Accepted Date:** 14 January 2022; **Published Date:** 21 January 2022

Abstract

The prevalence of Atopic dermatitis (AD), like other allergic diseases, has been increasing all over the world. AD affecting mostly children has been reported to have an incidence as high as 25%. Symptoms of itchiness, redness, inflammation and infections are giving unbearable suffering to the child and parents.

The standard treatment of using steroids to gain reasonable results is not the absolute solution because of disease fluctuations, chronicity and adverse effects. Pediatricians tend to look for alternative, unconventional treatments as supplementary measures.

The common varieties include herbal therapy used either systemically or topically, and therapeutic medicinal baths.

This commentary describes how a herbal formula consisting of five herbs was created for the treatment of AD. *In-vitro* and *in-vivo* experiments offered evidences of anti-inflammation, and anti-allergic effects. Two carefully planned clinical trials gave early confirmations of its effects against AD.

Of the five herbs, two were found to be most effective after biological assessments. This pair was selected to form, together with another antibacterial herb, a three herbs formula for topical application.

With regard to herbal baths for AD, coal-tar was compared with green tea for their soothing effects. Coal-tar was found superior to green tea.

Although more in-depth studies need to the completed in future, one could confidently encourage specialists and lay people alike, when facing difficulties with AD, herbal alternatives, either used systemically or topically could be considered.

Key Words: Atopic Dermatitis; Herbal treatment; Herbal bath.

Introduction

Allergic conditions have been a big challenge to physicians. The prevalence of allergic diseases, ranging from allergic rhinitis, asthma and atopic dermatitis has been reported to be increasing in both developed and developing countries [1,2]. Atopic dermatitis (AD) affecting mainly children of varying ages is considered the most common chronic skin disease, affecting up to 25% of children, especially in their first five years [3,4]. In addition, a high percentage of the early childhood cases would turn chronic

towards adulthood [5,6]. The allergic skin condition gives itchiness, redness, inflammation, infections, blisters and crusting which give unbearable sufferings to the child.

Although the predisposing cause of the condition AD is undoubtedly allergy, the chronic, long lasting presentations would lead to other pathological changes of the skin which include: inability to retain moisture and susceptibility to bacterial infections which complicate clinical treatments [7,8].

The current advocated treatment always includes immunosuppressive agents like steroids, mostly used topically and sometimes systemically. The responses could be good but recurrences and chronicity are inevitable. Other considerations like infection control and skin moisture preservation are useful sometimes but the overall outlook for allergic dermatitis cannot be over optimistic [9].

The relapsing nature of AD, in spite of energetic therapeutic attempts has invited different applications of unconventional treatment using medicinal herbs, in the form of topical agents, herbal baths or as oral drugs [10-12].

Our Pediatrician's Aspirations

The prevalence of relapses in AD must have invited our pediatrician's determination to explore for alternative treatment to supplement AD management.

Creating a Herbal Formula

We are aware of a remarkable clinical trial done in the United Kingdom 30 years ago for AD children using herbal decoctions prescribed by a Traditional Chinese doctor in London. The results of the herbal treatment have been impressive [13,14]. While we are not capable of getting the details of the herbal treatment, particularly with reference to subsequent experiences, we need to create our own herbal formula and protocol of clinical trial.

Historically, Traditional Chinese Medicine (TCM) practitioners have used a wide variety of medicinal herbs for the treatment of skin problems resembling AD. Careful studies of the recorded formulae and the component herbs allowed us to select those items that have been used repeatedly in the ancient records as favorable candidates. As a result, five herbs were identified as favorable choices for anti-allergic activities. The five herbs are:

Flos lonicerae, *Heba menthae, Cortex Moutan, Rhizoma atracylodis,* and *cortec phellodendric*, now labelled as "Pentaherb" (PHF) [15,16].

To prepare for further studies, the herbs are separately authenticated and specifically studied to rule out the possible presence of steroidal and related contents [17].

Laboratory Studies on the bioactivities of the formula Pentaherb

The main emphasis on the exploration of the bioactivities of PHF included its anti-inflammatory activities and specific influences on puritogemic cytokines like IL31 and alarmin IL33 when human eosinophils and dermal fibroblasts are activated [18,19].

In addition, human peripheral blood macrophages (PBNC) were incubated while the culture supernatant was analyzed for activities of anti-inflammation and release of gene-expression mediators against inflammation [20,21].

The *in-vitro* study results were very supportive of PHF's anti-inflammation and anti-allergic effects.

In the subsequent studies, three known chemical ingredient of PHF, viz. *gallic acid* from *Cortex Moutan*, *Chlorogenic acid* from *Flos Lonicerae* and *berberine* from *Cortex Phellodentric*, were demonstrated to have equivalent bioactivities of anti-inflammation and allergy suppression [22,23].

In-vivo studies using murine models of OXA induced dermatitis of the ear showed decreases in inflammation (redness and swelling) when Pentaherb was taken orally or applied topically. The evidence was further strengthened with the histological demonstration of eosinophilic responses [24].

Clinical Studies

Three clinical studies had been done since 2004.

The first one was a small pilot observational trial on only nine patients emphasizing on general clinical scores of disease severity and possible adverse effects. The standard scoring system for atopic dermatitis (SCORAD) before and 3 months after Pentaherb intake demonstrated good improvements. The favorable observations and absence of adverse effects encouraged proper clinical studies [25].

Two subsequent clinical trials deserve more detailed discussions.

Clinical Trial 1

Following a 2-weeks run-in period, children with long-standing moderateto-severe AD were randomized to receive a 12-week treatment with twice-daily dosing of three capsules of either PHF or placebo. The SCORing of Atopic Dermatitis (SCORAD) score, Children's Dermatology Life Quality Index (CDLQI), allergic rhinitis score, and requirement for topical corticosteroid and oral antihistamine were assessed before and at weeks 4, 8, 12 and 16 after treatment. Adverse events, tolerability, haematological and biochemical parameters were monitored during the study [26].

Eighty-five children with AD were recruited. Over 12 weeks of treatment, the mean SCORAD score fell from 58.3 to 49.7 in the PHF group (n = 42; P = 0.003) and from 56.9 to 46.9 in the placebo group (n = 43; P = 0.001). However, there was no significant difference in the scores at the corresponding time points between the two groups. The CDLQI in PHF-treated patients was significantly improved compared with patients receiving placebo at the end of the 3-months treatment and 4 weeks after stopping therapy (P = 0.008 and 0.059, respectively). The total amount of topical corticosteroid used was also significantly reduced by one-third in the PHF group (P = 0.024). No serious adverse effects were observed between the groups.

The result showed that PHF was efficacious in improving quality of life and reducing topical corticosteroids in children with moderate-to-severe AD. The formulation was well tolerated [26].

Clinical Trial 2

Clinical Trial 2 was preceded by the investigations on the effects of PHF on the cytotoxicity and proliferation of phytohaemagglutinin (PHA)- and staphylococcal enterotoxin B (SEB)-stimulated peripheral blood mononuclear cells (PBMC) isolated from buffy coat of blood donors. PHF-induced immunomodulation for five inflammatory mediators in cultured PBMC was measured by reverse transcription–polymerase chain reaction and enzyme-linked immunosorbent assay. The effects of a 3-month, open-label study of PHF on circulating inflammatory mediators in children with AD were then assessed.

The addition of PHF to cultured PBMC reduced the supernatant concentrations of brain-derived neurotrophic factor (BDNF), interferon (IFN)-ϒ and tumour necrosis factor (TNF)-α in response to PHA, and BDNF and thymus and activation regulated chemokine (TARC) following SEB stimulation. PHF increased epithelial cell-derived neutrophil activating peptide-78 levels in culture supernatants. At the RNA level, PHF suppressed the transcription of BDNF, TARC, IFN-ϒ and TNF-α. 28 children with AD were treated with PHF for 3 months, and their mean plasma concentrations of BDNF and TARC decreased significantly from 1798 pg mL^{-1} and 824 pg mL^{-1} at baseline to 1378 pg mL^{-1} and 492 pg mL^{-1} (P = 0.002 and 0.013, respectively) upon study completion. We could conclude that PHF possessed *in-vitro* and *in-vivo* immunomodulatory properties that may mediate the clinical efficacy observed in AD treatment [26, 27].

After the completion of the two carefully planned clinical studies, we established a basic endorsement of the clinical value of the herbal medicine PHF. The improvement in the quality of life of the allergic patients and their lessened dependence on cortical steroids had been well demonstrated. However, it was also obvious that the herbal treatment did not result in significant decrease in the severity of AD itself [27].

Pooling the clinical results of two separate clinical trials on two separate groups of 107 patients in total, strong evidence of improvement in the quality of life (DLQI) was achieved (p = 0.039) (Fig 1). With regard to the more objective SCORAD analysis, only an obvious trend of improvement not reaching statistical significance was observed.

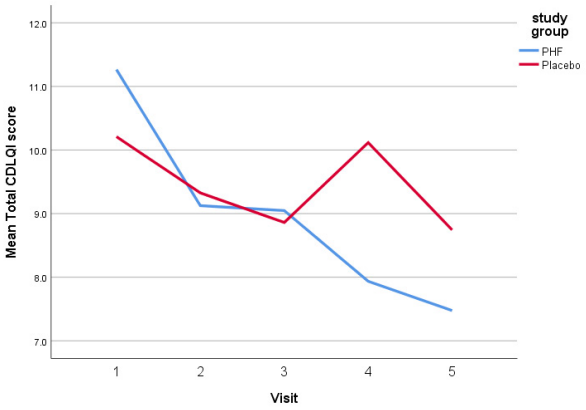

Figure 1: Changes of Quality of Life (CDLQI) score of the combined group of patients at each visit.

Further Studies related to the dosage and in-depth analysis of the chemical nature of the herbal formula would be necessary.

Before additional studies could be arranged, the pediatrician remained keen to explore for other means to supplement standard therapeutic practices.

Body Bath for Atopic Dermatitis

The mainstay of treatment for AD has been the regular application of emollients and topical anti-inflammatory medications since AD is basically a complex disorder involving varying degrees of skin inflammation, pruritus, erythema, dryness and infection. Caretakers are well aware of the excellent soothing effects of body bath given to the AD children [28, 29].

Traditionally, plant products have been used in body baths, as bath oils containing e.g. Pine-tar and green tea extracts. Pine-tar is derived from pine. It carries a pleasant smell and is believed to contain anti allergic ingredients, probably related to high polycyclic aromatic hydrocarbon. Likewise, green tea is believed to carry anti-allergic properties when used topically or even when drunken orally [30-33].

Our pediatricians wanted to test the efficacy of pine-tar or green tea when used in body baths for the AD children.

The efficacy of two complementary bath products was studied and compared. Efficacy and acceptability of the bath products were measured by patients' general acceptability of treatment (GAT: very good, good, fair or poor), disease severity (SCORAD:

SCoring Atopic Dermatitis), quality of life (CDLQI: Children Dermatology Life Quality Index); and the pertinent clinical parameters, measured before and after four weeks of treatment. In one group, nine AD patients were subjected to bathing with a pine-tar bath oil for 10 –15 min daily for four weeks. In another group, 20 AD subjects were bathed with warm water containing green tea extracts for four weeks. Results showed significant improvements in clinical- and patient-orientated parameters in the pine-tar bathing group, but less so in the green tea bathing group. Both groups reported very good or good GAT results while the pine-tar bath was much more outstanding. Green tea bathing was considered not as efficacious and would not be recommended for further clinical trials. Conclusions have therefore provided reasonable preliminary data on the efficacy of pine-tar bath for AD patients [34].

Discussion

The use of TCM among children suffering from AD is very common in China and Asia. The high percentage of AD patients known to be concomitantly suffering from other allergic conditions like allergic rhinitis further encourages alternative treatment like herbal medicine and body baths [35].

There exists suspicions that the herbal products might contain steroidal compounds that could function like steroids. In our carefully planned clinical studies, we applied advanced phytochemical procedures to investigate the herbs used, with the intension of strictly ruling out steroidal compounds. Subsequently, we confidently proved that the soothing effects provided to the AD patients were not steroidal [36].

Given the complex nature of AD itself, although our laboratory platform studies managed to demonstrate anti-inflammatory and anti-allergic effects, we remain speculative on the exact mechanisms of action.

On the clinical side, using the highly recognized assessment tools of SCORAD which is more objective and Quality of Life evaluation (DLQI) which is more subjective and qualitative, we could confirm that the qualitative effects given by the herbs appeared much better demonstrated than the objective. The most soothing effects occurred in the area of decreased steroidal dependence which parents are particularly concerned [37].

Body bath represents another common practice tracing back from the "Folk practice" days to contemporary. Evaluations on the effects of body bath on AD patients is more difficult than testing the systemic use of herbal formulations. The use of bath additives deserves proper evaluations, but again, general influences like environmental conditions, loving care from parents and other affections might seriously affect the results.

One thing that may be related to body bath is the use of special bodily apparels to keep the AD child warm while avoiding itchiness and desiccating. Such bodily apparels could be coupled with special considerations of drug delivery such as nanotechnology [38].

We have started preliminary explorations on using special material for body covers (sleeves and pull-overs) using microcapsules containing the ideal chemical or herbal extracts to maintain a slow but constant delivery [39]. This approach could be included in scientific considerations of household management for the relief of AD symptoms.

Developing a Topical agent derived from PentaHerb Formula

An on-going study is described as follows. Given the promising results of PHF as have been demonstrated in the laboratory with regard to anti-inflammatory and counter-allergic activities, it is logical to consider developing a topical agent related to the five herb formula.

In-vitro mechanistic studies suggested that PHF could suppress inflammatory meditators released from mast cells [20]. Our further bench experiments have indicated that Moutan Cortex and Menthae Herba are the two most effective herbs in suppressing mast cell mediator release. Presumably these two herbs could be mainly responsible for the anti-allergic effects of PHF [40,41]. Moutan Cortex and Menthae Herbs, when used together with another herbal item that possesses anti-bacterial ability, will complete a logical triple partnership in the topical formulation.

Calendula officinalis L. has been known to possess bactericidal effects and is popular in Europe [42,43]. Hence the topical formula to be studied for topical anti-allergic effects is planned to be composed of Moutan Cortex, Menthae Herba and *Calendula* in the ratio of 1:1:1.

An extensive study has demonstrated that the novel herbal formula at non-toxic doses exhibited immunosuppressive and anti-inflammatory activities and promoted cell migrations *in-vitro*. *In-vivo* study using oxazolone-induced atopic dermatitis-like mouse model has confirmed the inhibitory effects of the formula on the ear redness, swelling and itchiness without toxic effects. H&E and toluidine blue staining of the challenged ear tissues demonstrated that the triple-herbs formula decreased the epidermal thickness and mast cells proliferations [44]. AQP3, a water transporter, was significantly increased in oxazolone challenged ear tissues upon the treatment with the triple-herbs formula. Furthermore, Transdermal experiments showed that the triple-herbs formula could successfully penetrate through porcine ear skin. Subsequently, *in-vitro* skin toxicity testes have proven that the formula did not exhibited toxic effects on skin in the tested dosages.

Swelling consequent to increased scratching and skin

thickness is often the first hallmark of skin irritation and local inflammation, which are the indications of a number of processes during skin inflammation, such as increased vascular permeability, edema within the dermis, and epidermal hyperplasia. Our early results on mouse models showed that the triple-herbs formula significantly reduced ear swelling, epidermal thickness and itchiness (demonstrated from the scratching behavior). These findings suggested that the triple-herbs formula exhibited effective suppressive effects on skin irritation and anti-inflammatory activity *in-vivo*.

The key factor concerning skin hydration and cellular integrity is the presence of AQP, which acts mainly as selective-water pores. AQP3 could serve as a predominant water holder in the human skin, allowing glycerol to move into the more superficial layers of the epidermis. Inhibition of AQP3 activity happens in allergic dermatitis resulting in a significant decrease in epidermal water transport [45,46].

The AQP3 increase after the triple-herbs formula treatment indicated the positive epidermal water transport alterations in response to the herbal treatment.

The triple-herbs formula application on the mouse model of AD offered convincing evidences that it would be a favorable topical agent to supplement other topical agents.

Conclusion

The complex etiology of AD has negatively affected its management. The tendency of fluctuating responses to treatment, chronicity and frequent co-existence of other allergic conditions have further intensified the uncertainties of treatment applications. Although steroidal applications offer rather straightforward controls, their suspected adverse effects discourage long-term uses.

The use of complementary alternative management has been a common practice among family members and even the attending physicians.

We have critically studied the rationale and biological evidences of some of the popular alternative supplements: from herbal therapy used systemically and topically, to special treatment baths. We found sufficient evidences to encourage physicians and lay people alike, when facing difficulties with AD, they could consider those alternatives.

Acknowledgement

This work was supported by the State Key Laboratory Fund provided by the Innovation and Technology Commission of Hong Kong.

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