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ORIGINAL ARTICLE

Effect of rosmarinic acid on atopic dermatitis

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ABSTRACT

Rosmarinic acid is known to have anti-inflammatory and immunomodulatory activities. This study was performed to evaluate the effect of rosmarinic acid on atopic dermatitis (AD), one of the inflammatory disorders of the skin. Twenty-one subjects (14 women and seven men, 5–28 years of age) with mild AD participated in this study. Rosmarinic acid (0.3%) emulsion was topically applied to the elbow flexures of AD patients twice a day (once in the morning and once in the evening). All subjects were evaluated for skin conditions before treatment at the first visit, and then at 4 and 8 weeks after treatment. According to local Severity Scoring of Atopic Dermatitis index results, erythema on antecubital fossa was significantly reduced at 4 and 8 weeks ($P < 0.05$). Transepidermal water loss of the antecubital fossa was significantly reduced at 8 weeks compared to before treatment ($P < 0.05$). The results from self-questionnaires on the efficacy of rosmarinic acid indicated that dryness, pruritus and general AD symptoms improved. Our investigation into the AD-mitigating effect of rosmarinic acid through *in vivo* experiments demonstrated the possible clinical use of rosmarinic acid as a therapeutic agent for AD.

Key words: atopic dermatitis, pruritus, rosmarinic acid, transepidermal water loss.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that occurs most commonly during early infancy and childhood and is characterized by a chronically relapsing course. Although the pathogenesis of AD is not fully understood, it has been reported that AD is associated with multiple immunological abnormalities.[1,2]

Symptoms of AD induced by various signal transduction pathways mostly include inflamed skin damage and skin dryness. Accordingly, the generally accepted treatment includes moisturizers and topical steroids that maintain the moisture level in the skin and suppress inflammatory reactions, respectively. However, when used topically for prolonged periods, steroid hormones have been known to induce adverse side-effects.[3] In addition, cyclosporin A and FK506, which are used as non-steroidal therapeutic agents, have been reported to induce cutaneous T-cell lymphoma,[4] fever,[5] extreme rises in serum alkaline phosphatase in children,[6] enhanced irritation,[7] relapsing Kaposi's varicelliform eruption,[8] and so on. Therefore, at present, many researchers are actively trying to develop therapeutic agents that have high anti-inflammatory effects with few side-effects.

Rosmarinic acid (α-o-caffeoyl-3, 4-dihydroxyphenyl lactic acid) is a naturally occurring hydroxylated compound (Fig. 1) that has a broad range of applications, from food preservatives to cosmetics; it has also been applied to medicinal use, by virtue of its antimicrobial and antioxidant activities.[9–11] In addition, rosmarinic acid has the ability to block complement fixation, inhibit lipoxygenase and cyclooxygenase activity,[12–14] and suppress IKK-β downstream signaling in the tumor necrosis factor (TNF)-α-induced upregulation of CCL11, which is a potent chemoattractant and an activator of eosinophils, basophils, and T-helper cell (Th)2 lymphocytes.[15]

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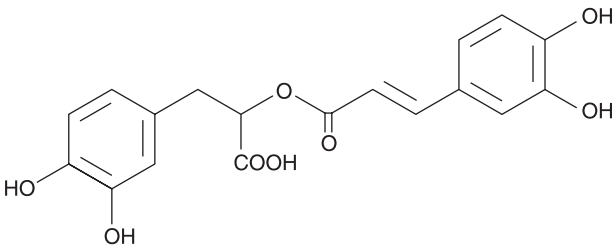

Figure 1. Structure of rosmarinic acid (α-o-caffeoyl-3,4-dihydroxyphenyl lactic acid).

Based on these reports, we investigated the effect of rosmarinic acid on atopic dermatitis.

METHODS

Products

Oil-in-water cream with or without rosmarinic acid was tested. The cream contained several principal ingredients: glycerin, methylparahydroxybenzoate, phenoxyethanol, xanthan gum, squalane, polysorbate 80, and beeswax. Cream with or without rosmarinic acid (0.3%) was applied to the elbow flexures twice daily for 4 and 8 weeks.

Subjects

Twenty-one subjects (14 women and seven men; average age, 15.1 ± 3.1 years) were recruited at Dermapro Skin Research Center (Seoul, Korea), and participated in this study. Because they were affected by eczematous lesions on the elbow flexures, these subjects were clinically graded as having moderate atopic dermatitis according to the guidelines for the Severity Scoring of Atopic Dermatitis (SCORAD) index. This study was conducted in accordance with the intent and purpose of the Good Clinical Practice Regulations described in the US Code of Federal Regulations (Title 21, Parts 50, 56, and 312) and/or the Declaration of Helsinki. Written consent was obtained in each case. A double-blind, vehicle-controlled, randomized half-elbow flexure trial was performed to evaluate the clinical effects of cream containing 0.3% rosmarinic acid on AD patients over a 2-month period. Rosmarinic acid (0.3%)-containing cream was applied to the elbow flexures twice a day (once in the morning and once in the evening). Topical or systemic use of corticosteroids was strictly prohibited during the study period. For all subjects, the diagnosis of AD was established according to the criteria of Hanifin and Rajka (scoring atopic dermatitis) protocol comprising six intensity items: (i) erythema/darkening; (ii) edema/population; (iii) oozing/crust; (iv) excoriations; (v) lichenification/prurigo; and (vi) dryness. Each item was graded by on a four-point scale: 0, absent; 1, mild; 2, moderate; and 3, severe.[16]

Clinical evaluation

Rosmarinic acid (0.3%) cream was applied to the elbow flexures twice daily (once in the morning and once in the evening) for 8 weeks. All subjects were evaluated for skin conditions at the first visit before treatment and then at 4 and 8 weeks after treatment. The evaluation methods included clinical assessments (SCORAD), instrumental assessments (transepidermal water loss [TEWL]) and self-assessments. The symptoms and degree of AD were assessed objectively through clinical evaluation using the SCORAD index as presented by the consensus report of the European Task Force on Atopic Dermatitis.[17] TEWL was measured by Tewameter (Courage + Khazaka, Koln, Germany) before treatment and at 4 and 8 weeks after treatment at the antecubital fossa, and self-assessments were completed by questionnaire.

Safety evaluation

The safety of the sample was assessed by clinical examination by a dermatologist at 4 and 8 weeks. This assessment took into consideration the elements reported by subjects (subjective and objective signs), as well as those noted by the dermatologist (clinical signs). The frequency, duration and intensity of the signs and a possible relationship with the tested products were investigated. The subjective signs included itching, stinging, burning, stiffening and tightening, and objective signs included redness, edema, scale and papule.

Statistical analysis

All statistical analyses were performed by ANOVA with StatView Statistical Package ver. 5.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

Table 1. Clinical assessment

Items	0 weeks	4 weeks	8 weeks
Erythema			
Group A	0.68 ± 0.2301	0.58 ± 0.2334	0.63 ± 0.2321
Group B	1.11 ± 0.2524	0.74 ± 0.2274*	0.53 ± 0.1772*
Edema/papulation			
Group A	0.68 ± 0.2301	0.63 ± 0.2053	0.68 ± 0.2031
Group B	0.95 ± 0.2475	0.68 ± 0.2170	0.53 ± 0.1930*
Oozing/crust			
Group A	0.53 ± 0.2076	0.26 ± 0.1683	0.32 ± 0.1719
Group B	0.89 ± 0.2524	0.42 ± 0.1922*	0.32 ± 0.1718*
Excoriation			
Group A	0.42 ± 0.1922	0.47 ± 0.2076	0.53 ± 0.2076
Group B	0.58 ± 0.1763	0.42 ± 0.1922	0.47 ± 0.1930
Lichenification			
Group A	1.37 ± 0.1906	1.21 ± 0.1961	0.89 ± 0.2149*
Group B	1.47 ± 0.2076	1.26 ± 0.2142*	0.89 ± 0.2139*
Local pruritus			
Group A	1.21 ± 0.2712	0.84 ± 0.2327*	0.58 ± 0.2068*
Group B	1.37 ± 0.2560	0.79 ± 0.2240*	0.53 ± 0.1772*
TEWL			
Group A	16.67 ± 2.1473	17.02 ± 1.9432	17.59 ± 2.0818
Group B	20.08 ± 2.5512	16.57 ± 1.8642	14.62 ± 1.7884*

Group A, cream; group B, rosmarinic acid (0.3%) cream. Data are expressed as means ± standard error. *$P < 0.05$. TEWL, transepidermal water loss.

RESULTS

The severity of AD before and after treatment with rosmarinic acid was scored in 21 patients. The mean SCORAD index decreased from 7.37 ± 0.32 before treatment to 3.27 ± 0.21 after treatment with rosmarinic acid-containing cream for 8 weeks ($P < 0.05$). However, in the control group (cream only), no significant change of SCORAD score was observed (before treatment, 6.49 ± 0.81; after treatment for 8 weeks, 5.63 ± 0.97). As shown in Table 1, rosmarinic acid improved AD in patients with AD. Erythema and oozing/crust were significantly reduced after 4 weeks ($P < 0.05$) and edema on the antecubital fossa was significantly reduced after 8 weeks ($P < 0.05$). Rosmarinic acid did not have a significant effect on excoriation. Lichenification and local pruritus were significantly reduced after 8 weeks in group B (rosmarinic acid 0.3%) more than in group A (cream only), although the cream used as a negative control also significantly reduced these symptoms. In the TEWL study, the TEWL of the antecubital fossa was significantly reduced after 8 weeks ($P < 0.05$). In addition, the results of self-questionnaires on the efficacy of rosmarinic acid indicated that rosmarinic acid improved dryness, pruritus and general AD symptoms (data not shown). In safety tests, there were no reactions in any patients based on the 4- and 8-week readings. That is, we did not observe any adverse reactions, such as erythema, burning and pruritus, related to the use of rosmarinic acid in study patients. Rosmarinic acid cream was considered safe for use in AD patients.

DISCUSSION

As previously mentioned, despite the effectiveness of steroid hormones in treating AD, steroid hormones can induce various side-effects such as skin atrophy, dilation of blood vessels, depigmentation, and so on.[3] Therefore, this study was designed to evaluate whether rosmarinic acid can be used as an alternative or adjuvant therapeutic agent for AD instead of steroid hormones. To this end, *in vivo* experiments were performed. In this report, we described the characterization of rosmarinic acid as a possible AD-mitigating agent.

After treatment with rosmarinic acid, we observed a statistically significant reduction of SCORAD score, decrease in pruritus and decrease in TEWL, indicating that rosmarinic acid can be introduced as a therapeutic agent for AD. There were no reactions in any

patients in the patch test, suggesting that rosmarinic acid can safely be applied to human skin and possibly be safely applied to patients with AD. However, understanding of the precise molecular mechanisms by which rosmarinic acid improves AD remains incomplete.

A recent report that the transcriptional and translational expression levels of CCL11 and CCR3 were significantly increased in lesional skin from AD, but not in non-atopic controls, indicates the involvement of CCL11 in the pathogenesis of AD.[18] Recent experiments based on conditional IKK-β loss-of-function mutations indicate that IKK-β activity is required for the inactivation of a severe inflammatory reaction that leads to multi-organ failure in response to ischemia-reperfusion.[19] IKK-β activity is also required to prevent a considerable number of different cell types from undergoing apoptosis.[20] In our previous study, we found that rosmarinic acid inhibits tumor necrosis factor-α-induced production of CCL11 and CCR3 and that this action is mediated through inhibition of IKK-β.[15] Based on these results, we suggest that rosmarinic acid ameliorates symptoms of AD through suppression of IKK-β.

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