

Application of Topical Madecassoside Cream in Dogs and Cats with Skin Diseases

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Abstract : Madecassoside, an active ingredient extracted from *Centella asiatica*, is used for treatment of various skin disorders in humans. However, the effect of madecassoside on the skin of dogs and cats has not been studied yet. The purpose of this study was to evaluate clinical efficacy of topical madecassoside cream in dogs and cats with skin diseases. A total of twenty-one dogs and ten cats with various skin diseases were included in the study. The 1% topical madecassoside cream was applied to the animal's skin lesion at least once a day for 7 days, and the skin condition was evaluated before the application of madecassoside cream (day 0) and 7 days after the application (day 7). The skin condition was scored by five clinical indices: canine atopic dermatitis extent and severity index-4 (CADESI-4), coat condition, pruritus, scale, and general condition. In dogs, all five clinical indices (CADESI-4, coat condition, pruritus, scale, and general condition) were significantly decreased on day 7 compared to those on day 0 ($p < 0.0001$, $p < 0.05$, $p < 0.001$, $p < 0.01$, and $p < 0.05$, respectively). In cats, the CADESI-4 and scale were significantly decreased on day 7 compared to those on day 0 ($p < 0.01$ and $p < 0.05$, respectively). No adverse effects were observed during the trial period in the dogs and cats included in this study. The results of this study demonstrate that the topical madecassoside cream is applicable to skin lesions in dogs and cats.

Key words : madecassoside, topical cream, skin disease, dogs, cats.

Introduction

As the number of companion animals increases, the number of companion animals suffering from dermatologic problem is also increasing. According to a recent study, skin disease was the leading cause of animal hospital visits (5). Bacterial and fungal infections are considered to be the most common causes of skin diseases, and also include parasitic infections, allergic skin disease, and skin tumors (8,14). Therefore, oral and topical therapeutics for the treatment of such skin diseases are very commonly used in companion animals.

Despite the fact that various treatment agents can effectively improve skin diseases, many side effects may occur by those drugs. In dogs, the appearance of various antibiotic-resistant bacteria is frequent (20), and this is thought to be due to the long-term use of empirical antibiotics to treat canine

pyoderma. In addition, chemical anti-fungal agents are frequently used in veterinary hospitals to treat fungal infection, resulting in drug interactions, nausea, vomiting, anorexia, and liver damage (1). Steroids are the most commonly used drugs for allergic skin diseases, however long-term use of steroids resulted in obesity, polyuria and polydipsia, urinary tract infection, hepatic abnormalities and immunosuppression (13,18).

Madecassoside, an active compound extracted from *Centella asiatica*, is a pentacyclic triterpene saponin with multiple pharmaceutical potentials (4,17). In humans, madecassoside is widely used for treatment of various skin diseases such as acne, baldness, vitiligo, atopic dermatitis, psoriasis and skin wounds because of its therapeutic and relieving effects on skin (7,17).

However, the effect of madecassoside on skin has not been studied yet in dogs and cats. Since madecassoside is a natural ingredient extracted from plant, it is expected to improve skin lesions effectively without serious side effects shown in existing chemical drugs. This is a multicentric pilot study to evaluate the feasibility of applying topical madecassoside cream to dogs and cats with various skin diseases.

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Table 1. The clinical indices used to score skin condition in this study

Clinical indices	Score	Definition
CADESI-4 (11)	0~180	Three lesions (erythema, lichenification and alopecia/excoriation) were scored from 0 to 3 at various skin sites.
Coat condition (10)	0	Normal coat
	1	Dull coat but no broken hairs
	2	Dull coat with evidence of broken hairs
	3	Hair loss over < 10% of body surface area
	4	Hair loss over 10-25% of body surface area
Pruritus (12)	0-1	Not pruritic at all, or scratches occasionally like a normal animal
	2	Scratches/bites occasionally, and is generally comfortable
	3	Scratches and bites frequently, but not excessively
	4	Scratches and bites very frequently, often seems uncomfortable
	5	Scratches and bites almost constantly, in a lot of discomfort
Scale (9)	0-1	Almost normal
	2	Mild
	3	Moderate
	4	Severe
General condition (10)	0	Appetite, sleep and exercise patterns normal
	1	Appetite, sleep and exercise patterns affected < 5% of the time
	2	Appetite, sleep and exercise patterns affected < 10% of the time
	3	Appetite, sleep and exercise patterns affected 10% to < 25% of the time
	4	Appetite, sleep and exercise patterns affected 25% to < 50% of the time
5	Appetite, sleep and exercise patterns affected > 50% of the time	

CADESI-4, coat condition, and general condition indices were used from previous studies (10,11).

Pruritus and scale indices were used with some modification of previous studies (9,12).

Materials and Methods

Study design

This evaluation included the efficacy of topical madecassoside cream, which was previously approved from Korean Animal Health Product Association, before and after application in dogs and cats with skin diseases. The client-owned dogs and cats from animal hospitals were enrolled in the clinical trial. Informed, written consent was obtained from each animal's owner prior to the enrolment.

Animals

Dogs and cats with skin lesions were included in the trial based on the evaluation by veterinarian. The category of skin lesions or diseases included: skin lesion by allergic dermatitis, bacterial and/or fungal infection, wound-related dermatitis, keratinization disorders including seborrheic dermatitis, dry skin, autoimmune skin disorders, alopecia, feline acne, and other skin diseases diagnosed by veterinarian.

Application of madecassoside cream

The 1% topical madecassoside cream was applied to the animal's skin lesion at least once a day for 7 days, and the skin condition was evaluated by veterinarian before the application of madecassoside cream (day 0) and 7 days after the application (day 7). No systemic or topical treatments other than madecassoside cream were applied to the dogs and cats during the trial period.

Clinical assessment

The clinical efficacy of madecassoside cream on skin lesion was assessed and scored by five clinical indices—canine atopic dermatitis extent and severity index-4 (CADESI-4), coat condition, pruritus, scale, and general condition—based on the previous studies (9-12) (Table 1).

In addition, to evaluate possible hepatotoxicity of madecassoside cream, results of liver enzyme test—alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP)—on day 0 and day 7 were obtained from medical records if available.

Statistical analysis

All data were shown as the mean \pm standard deviation. Changes in clinical scores between day 0 and day 7 were compared using the Wilcoxon matched-pairs signed rank test. Statistical analysis was performed using the Prism 9 software (GraphPad Software, San Diego, CA, USA). A p-value less than 0.05 was considered statistically significant.

Results

Animals

Twenty-one dogs and ten cats with skin diseases were enrolled in the study. The clinical characteristics of the dogs and cats included in this study are shown in Table 2. Dogs and cats with various ages were included, ranging from 4 months to 15 years in dogs and 2 to 13 years in cats. All

Table 2. The clinical characteristics of the dogs and cats included in this study

Species	Variables	Results
Dogs (n = 21)	Age, year	7.75 ± 3.89
	Body weight, Kg	5.58 ± 5.37
	Male/female, n	9/12
	Breed, n	
	Maltese	7
	Poodle	4
	Shih Tzu	3
	Mixed	3
	Yorkshire Terrier	2
	Pekingese	1
Standard Poodle	1	
Cats (n = 10)	Age, year	5.70 ± 2.98
	Body weight, Kg	4.93 ± 0.65
	Male/female, n	6/4
	Breed, n	
	Korean Short Hair	4
	Mixed	1
	Munchikin	1
	Persian	1
	Russian Blue	1
Siamese	1	
Turkish Angora	1	

Continuous variables were expressed as means ± standard deviations.

Table 3. The diagnoses of dogs and cats included in this study

Species	Diagnosis	Results, n
Dogs (n = 21)	Atopic dermatitis and/or food allergy	14
	Atopic dermatitis with secondary infection	3
	Pyoderma	2
	Fungal dermatitis	1
	Seborrhea	1
Cats (n = 10)	Atopic dermatitis	2
	Seborrhea	2
	Footpad hyperkeratosis	2
	Atopic dermatitis with secondary infection	1
	Footpad eczema	1
	Pyoderma	1
	Psychogenic alopecia	1

dogs were small breed dogs except for one Standard Poodle dog, and the most common breed was Maltese (n = 7), followed by Poodle (n = 7), Shih Tzu (n = 7), and Mixed (n = 7). In cats, the most common breed was Korean Short Hair (n = 4).

The diagnoses of dogs and cats included this study were classified according to similar categories (Table 3). Dogs with atopic dermatitis and/or food allergy were the most common (n = 14), followed by dogs with atopic dermatitis and concurrent secondary infection (n = 3). In cats, atopic dermatitis (n = 2), seborrhea (n = 2), and footpad hyperkeratosis (n = 2) were the most common.

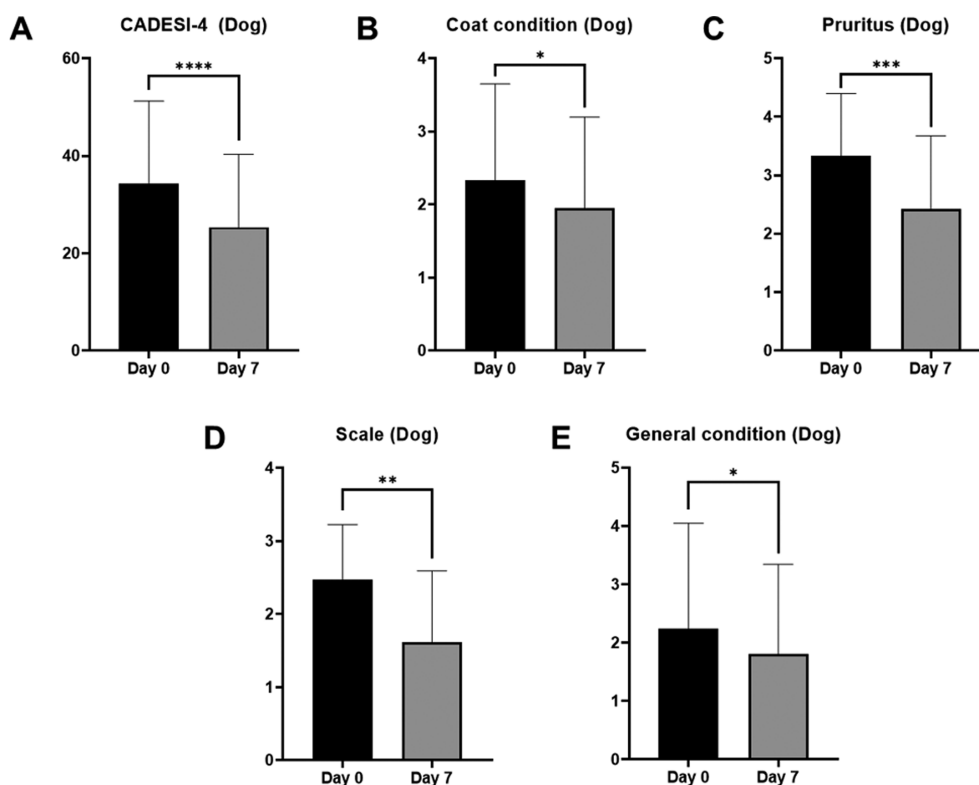


Fig 1. Change in clinical scores of skin condition in dogs included in this study. Significant reductions of clinical score in (A) CADESI-4, (B) coat condition, (C) pruritus, (D) scale, and (E) general condition indicate improvement of skin condition after application of madecassoside cream. ****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05. CADESI-4, canine atopic dermatitis extent and severity index-4.

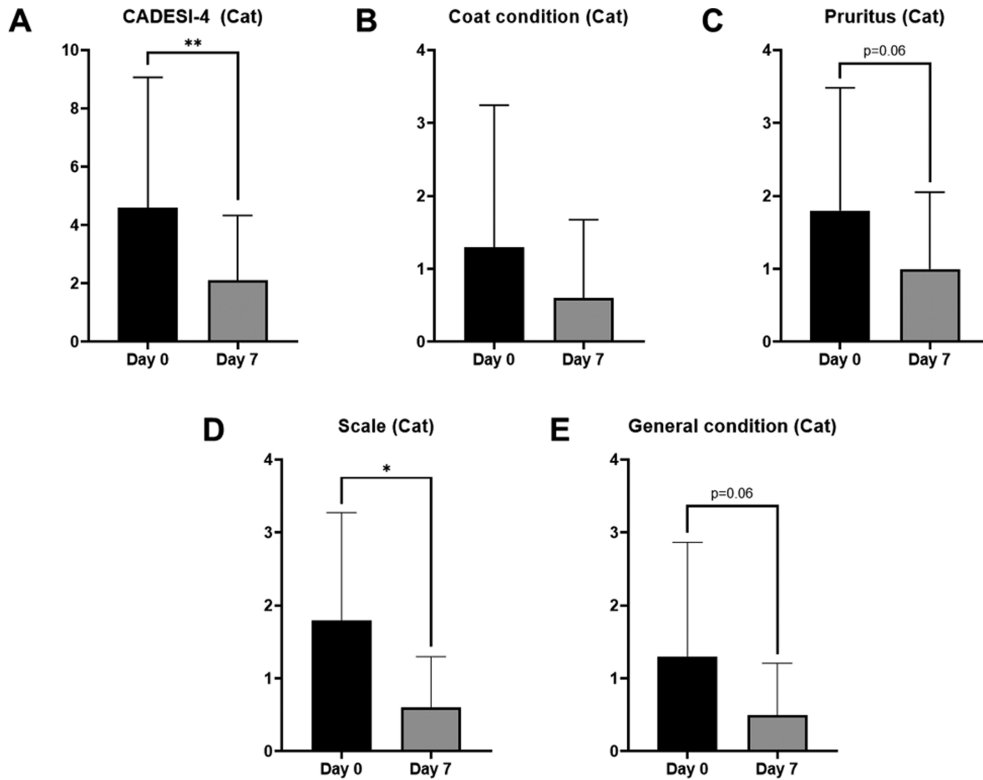


Fig 2. Change in clinical scores of skin condition in cats included in this study. The clinical scores were evaluated based on the five clinical indices: (A) CADESI-4, (B) coat condition, (C) pruritus, (D) scaling, and (E) general condition. Significant reductions of clinical score in (A) CADESI-4 and (D) scale indicate improvement of skin condition after application of madecassoside cream. ** $p < 0.01$, * $p < 0.05$. CADESI-4, canine atopic dermatitis extent and severity index-4.

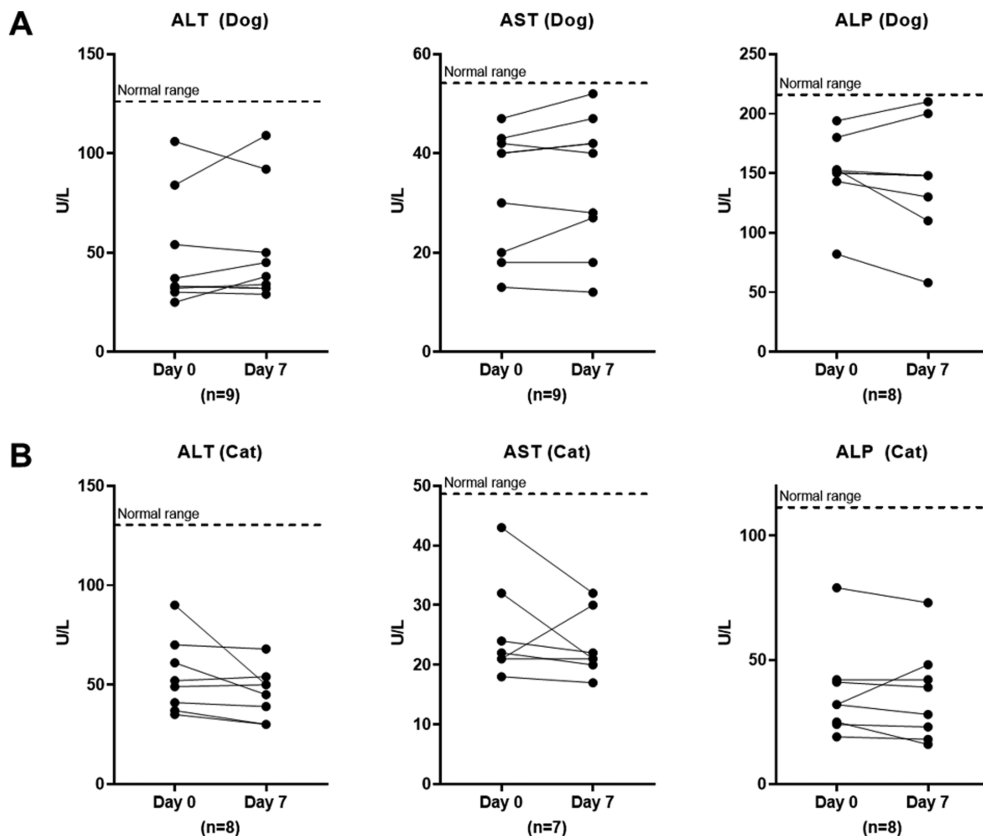


Fig 3. The results of liver enzyme tests obtained from medical records of dogs and cats included in this study. All results remained within normal range during the trial period. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Clinical outcome

The clinical scores of skin condition were evaluated on day 0 and day 7 based on the five clinical indices: CADESI-4, coat condition, pruritus, scale, and general condition.

In dogs, the CADESI-4 score was significantly decreased on day 7 compared to that on day 0 ($p < 0.0001$), showing mean reduction rate of 26.19% (Fig 1A). The coat condition score was significantly decreased on day 7 compared to that on day 0 ($p < 0.05$), showing mean reduction rate of 16.33% (Fig 1B). The pruritus score was significantly decreased on day 7 compared to that on day 0 ($p = 0.0001$), showing mean reduction rate of 27.15% (Fig 1C). The scale score was significantly decreased on day 7 compared to that on day 0 ($p = 0.0013$), showing mean reduction rate of 34.62% (Fig 1D). Lastly, the general condition score was also significantly decreased on day 7 compared to that on day 0 ($p = 0.0156$), showing mean reduction rate of 19.15% (Fig 1E).

In cats, the CADESI-4 score was significantly decreased on day 7 compared to that on day 0 ($p = 0.0078$), showing mean reduction rate of 54.35% (Fig 2A). The scale score was also significantly decreased on day 7 compared to that on day 0 ($p = 0.0156$), showing mean reduction rate of 66.67% (Fig 2D). The scores for coat condition, pruritus, and general condition on day 7 showed tendency to be decreased compared to those on day 0 (mean reduction rate of 53.85%, 44.44%, and 61.54%, respectively), however there were no statistical significance ($p = 0.125$, $p = 0.0625$, and $p = 0.0625$, respectively).

The results of liver enzyme test (ALT, AST and ALP) of dogs and cats included in this study were obtained from medical records of the animal's primary hospital. The results of ALT in nine dogs, AST in nine dogs and ALP in eight dogs on day 0 and day 7 were obtained, and all results remained within normal range during the trial period (Fig 3A). The results of ALT in eight cats, AST in seven cats, and ALP in eight cats on day 0 and day 7 were obtained, and all results remained within normal range during the trial period (Fig 3B).

Discussion

In this study, five clinical indices—CADESI-4, coat condition, pruritus, scale, and general condition—were used to evaluate the various effects of topical madecassoside cream on the skin lesion, and several different characteristics of madecassoside were identified in each of the indices.

The CADESI-4 score was improved after application of madecassoside cream in both dogs and cats. The CADESI-4 is an index that visually evaluates erythema, lichenification, excoriation, and/or alopecia (11). In previous studies (3,16), the extract of *Centella asiatica* improved re-epithelialization and wound healing of skin by promotion of skin keratinocyte migration, neovascularization, and expression of vascular endothelial growth factor, as well as suppression of interleukin-6 and tumor necrosis factor- α . This healing and anti-inflammatory effects of madecassoside are possible to have improved skin lesions such as erythema and excoriation in this study. In another previous study (19), extract of *Centella asiatica* increased collagen synthesis and also exhibited anti-bacterial, wound-healing effect in a rat. The

anti-bacterial activity by madecassoside might have improved the skin lesion of animals with bacterial infection in this study. This anti-bacterial effect of madecassoside cream will be of great help to dogs and cats in that it can reduce the abuse of antibiotics and also inhibit emergence of antibiotic-resistant bacteria in small animal medicine. In addition, a previous study reported that *Centella asiatica* activated hair growth and also increased expression of hair growth related genes in human dermal papilla cells (2). Thus, madecassoside may have potential to improve alopecic lesions in dogs and cats as well.

The pruritus, one of the most crucial clinical features of allergic skin disease, was significantly improved after application of madecassoside cream in dogs. The improvement of mean pruritic score was also observed in cats, although there was no statistical significance. In both dogs and cats in this study, allergic skin diseases including atopic dermatitis and food allergy were the most common skin disease. In a previous study in atopic dermatitis model mice (6), topical application of *Centella asiatica* reduced allergic inflammation response by suppression of several cytokines including interleukin-4 and interleukin-13, and also inhibited release of immunoglobulin E. This blockade of the key drivers of allergic response by madecassoside would have played a major role in improving the pruritus of dogs and cats. Since allergic skin diseases are common but difficult to manage in dogs and cats, the topical madecassoside cream is expected to be a novel and effective therapeutic agent for dogs and cats with allergic skin diseases, if its efficacy and safety are clearly proven in further studies.

Of the five clinical indices, the scale index showed the largest improvement rate in both dogs and cats in this study. In a prior in-vitro study (15), madecassoside enhanced the skin homeostasis and skin barrier function by anti-inflammation and skin hydration effects. In that study (15), the skin hydration was achieved by increase of aquaporin-3, loricrin, and involucrin in keratinocytes as well as hyaluronan secretion in dermal fibroblasts, which are major moisturizing factors of skin. The significant improvement of scale index in dogs and cats in this study is possible to have been contributed by skin hydration and barrier enhancement effect of madecassoside on skin. The skin hydration effect of madecassoside cream might also have improved pruritus in animals with atopic dermatitis or dry skin in this study.

In this study, the improvement of clinical indices was theoretically explainable by the previous studies of madecassoside. However, the mechanism of skin lesion improvement by madecassoside cream was not identified in this study, which needs to be verified through further studies. Meanwhile, the clinical manifestations or diagnoses of dogs and cats included in this study are skin diseases that can be easily encountered in animal hospitals, and the clinical efficacy of topical madecassoside cream was evaluated in actual clinical field, rather than the laboratory environment. Therefore, the topical madecassoside cream is expected to show practical and useful results in dogs and cats with various skin diseases, if further evaluation on its effect on specific skin diseases in a larger scale is properly done in the future. In addition, since all results of liver enzyme tests in dogs and

cats remained within normal reference range during the trial period, the topical madecassoside cream is considered to have less side effects compared to chemical drugs such as anti-fungal agents and steroids. However, since the clinical trial of this study evaluated only liver enzyme results for a short period of time, further safety evaluation for a longer period of time from more various aspects is necessary in order to safely apply madecassoside cream to dogs and cats.

There are several limitations in this study. First, the sample size of cats included in this study was relatively small. The lack of statistical significance in several clinical indices in cats is thought to be due to the small sample size. Secondly, dogs and cats with relatively mild skin diseases were included in this study, as shown in the low scores of clinical indices. In these animals with mild skin diseases, the improvement rates of clinical indices were less than 40% in dogs and less than 70% in cats. If used alone in dogs and cats with more severe skin diseases, the improvement rate of the madecassoside cream is expected to be lower than the result of the present study. Therefore, the topical madecassoside cream is considered to be a novel treatment option that can be useful to clinicians only when used as an adjuvant treatment for dogs and cats with various skin diseases.

Conclusions

To our knowledge, this is the first study to investigate clinical efficacy of topical madecassoside cream in dogs and cats with skin diseases. In this study, short-term application of the 1% topical madecassoside cream was able to improve skin lesions without other treatments in dogs and cats with various skin diseases. In addition, no adverse effects were observed in the liver enzyme test results after application of the madecassoside cream for 7 days. Therefore, the topical madecassoside cream is considered to be applicable to dogs and cats with various skin diseases, although further verification is required.

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