

Antipruritic armamentarium with short term nutritional support solution involving silymarin and curcumin for atopic dermatitis in dogs

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ABSTRACT

The present researcher group hypothesized that commercially available oral/topical solution involving *Curcuma Longa* and *Silybium marianum* combination will significantly decrease the pruritus scores after short-term (1 week of twice-daily) topical treatment in 26 dogs with atopic dermatitis. Evaluations included, mean day 0 Owner Pruritus Visual Analogue Scale score were similar ($p>0.05$) among the Silifort paste treatment groups (6.90 - 6.93 cm for Silifort paste treated animals (range 2-10) and placebo control dogs (range 2-10), respectively, in which continued to gradually reduce over the remaining 6 days of research in the Silifort paste treatment group ($p<0.0001$) and at day 7, decreased to 0.93 cm (a 6 cm reduction, which corresponds to a decrease from “severe itching” to “normal”). The mean day 0 Veterinarian Dermatitis Visual Analogue Scale score were similar ($p>0.05$) between the Silifort paste treatment group (6.70 - 6.75 cm for the Silifort paste treated animals (range 2-10) and placebo control dogs (range 2-10), respectively, whereas at day 7 decreased to 1 cm (a 5.75 cm decrease from “moderately severe dermatitis” to “normal”) and placebo control animals to 5.2 cm (a 1.5 cm decline from “moderately severe dermatitis” to “mildly moderate dermatitis”) ($p<0.0001$). Veterinarian Visual Analogue Scale dermatitis scores in Silifort paste treated animals were notably reduce compared to placebo control dogs on day 7 ($p<0.0001$). The present study supports a potential benefit of topical Silifort paste for short term relieving itching sensation. This treatment modality may replace immunosuppressive applications, with its anti-inflammatory, anti-infectious and antioxidant formulation.

INTRODUCTION

Silymarin, a herbal derived flavonoid, obtained from seeds and fruits from milk thistle (*Silybium marianum* L. Gaertn.), has been involved with the Asteraceae family Asteraceae (1). The latter milk thistle extract of milk thistle traditionally used for therapeutic armamentarium for several disorders (2), which is now under consideration for treatment of several dermatological disorders (3).

Curcumin involved as diferuloylmethane, has long been spice, turmeric. Turmeric has gained medicinal properties (4-6). In the present study both herbal treasures were used and it was hypothesized that commercially available oral/topical nutritional support solution involving *Curcuma Longa* and *Silybium marianum*, Silifort paste (Silp), (Aurora, Italy, Turkish side distributor Pharmax, Turkey) combination will significantly decrease the pruritus scores after short term (1 week of twice-daily) topical treatment in dogs with atopic dermatitis (Ad).

MATERIAL and METHODS

Demographics

All necessary data of was shown on table 1. with detailed demographic values. A total of 26 dogs were included to the study (Table 1).

Interpretation of analytic methods

Diagnosis was based on necessary testing, laboratory evaluation and deemed necessary applications shown at Table 2. To those of slowly 26 cases were deemed eligible without pyoderma, mycotic secondary infection, demodicosis/scabies or endocrine disorders. This study was approved by HADYEK with number of 2019/022.

Topical usage of Silp nutritional support

Commercially available nutritional support solution involving *C. longa* and *S. marianum* (Silifort pasta 30 gr, Aurora biofarma, Italy, Turkish side distributor Pharmax, Turkey); Silp was applied onto the lesional area(s) for a short term (1 week of twice-daily) topical treatment in dogs with Ad enrolled in this study. Control group dogs received setirizin (Zrytec oral drop) with 1 mg/kg dosage daily for a week.

CADESI-04 scores

Based on Hill's atopy index application by use of a iphone 8 plus device was recorded and obtained sum of data sent to e mail as a pdf file (automatically delivered by the application).

Statistical analysis

Treatment efficacy of the turmeric/Silymarin compared to placebo control dogs in the present study was assessed by the mean owner VAS pruritus via mean veterinarian VAS

Table 1. Baseline characteristics of enrolled dogs

Variable	Control group	Treatment group
Breed distribution [n(%)]		
Mixed breed	6 (60)	9 (56.2)
Purebred	4 (40)	7 (43.8)
Sex distribution [n(%)]		
Male	5 (50)	7 (43.8)
Female	5 (50)	9 (56.2)
Mean age [years (range)]	6.7 (2-13)	5.8 (1-12)
Mean weight at study onset [kg (range)]	17.3 (4-34)	16.7 (4-42)
Owner Pruritus VAS score at study onset [arithmetic mean (cm)]	6.90	6.93
Veterinarian Dermatitis VAS score at study onset [arithmetic mean (cm)]	6.70	6.75

Table 2. Diagnosis criteria of atopic dogs.

Observational criteria/parameter	Prelaud criteria	Favrot criteria	Hill's atopy index handphone application
Pruritus evaluation	Owner Pruritus VAS score at study onset [mean]	Veterinarian Dermatitis VAS score at study onset [mean]	Clinical exam
Testing	Polycheck in vitro allergen determination	Non-invasive monitoring	Dermatological examination
	Acetate tape impression, deep skin scraping, Dermlite D4 dermatoscopic exam	Excluding other relevant disorders (i.e. microbiological,mycological lab work, endocrine profile: i.e. total T4, plasma cortisol values within reference ranges)	

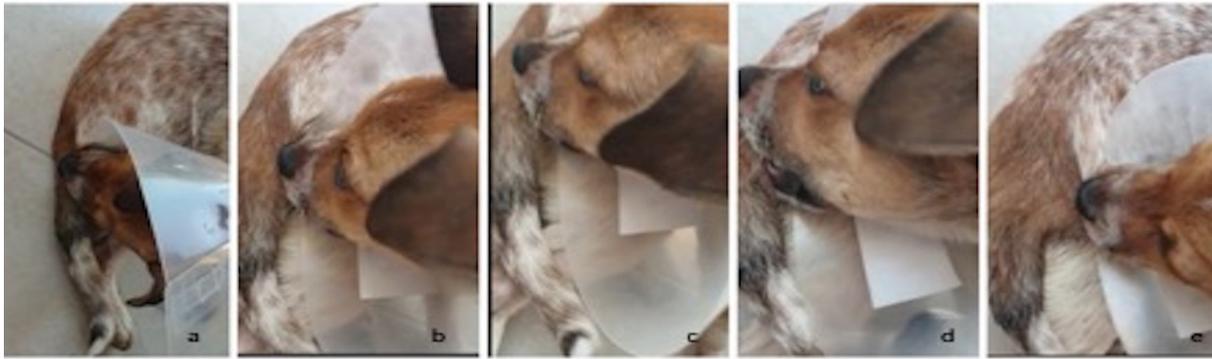


Figure 1. Slight view of pruritus behavior with in few seconds (a – e). Specifically dedicated to the gut microbiome which can modulate ‘gut-skin axis’, tryptophan existed out via gut microbiome could participate for the pruritus, as was the case herein showed. Several seconds thereafter showed itching sensation, licking, chewing behaviour with a pruritus score of 9. After Silp treatment of 1 week, score declined to 1.



Figure 2. Two different cases diagnosed with Ad, with pododermatitis and pruritus scores of 6 and 7, respectively. After Silp treatment scores were evident as 0 and 1, respectively score declined to 1.



Figure 3. End stage inflammation resulting in otitis externa due to allergic reaction and histamin intolerance in Ad. This case was presented with a pruritus score of 7, which gradually decreased to 1, after Silp treatment.



Figure 4. Ad has been extensively determined in our clinical practice within the small breeds; as the pruritus scores were 6, 4, 5 and 7, respectively with notably observed itching sensation..

dermatitis scores on daily basis for seven days and on day 0 and 7, respectively. Repeated measures ANOVA test were used to determine the time, group and group & time interactions. Friedman's two way-analysis of variance test were used to control the time interaction (days) for each group. To analyze the differences on each day between groups Mann-Whitney-U test were used and values <0.05 was recognized significant. All tests were done with package software (SPSS 22.0, SPSS Inc., USA)

RESULTS

Macroscopical view of selected cases

Owner VAS pruritus scores on each day of study

Mean 0. day owner VAS pruritus scores were similar ($p>0.05$) within the treatment groups (6.90 and 6.93 cm for the turmeric/silymarin treated dogs (range 2-10) and placebo control dogs (range 2-10), respectively. After 1 day of treatment, a 0.55 cm decrease of the mean owner VAS pruritus scores was observed in the treatment group, while the control dogs had a 0.27 cm reduction. The mean owner VAS pruritus scores continued to gradually reduction over the outstanding 6 days ($p < 0.0001$) of study in the treatment group. The

mean owner VAS pruritus scores in the turmeric/silymarin treated dogs were notably lower compared to placebo treated animals on days 3 ($p < 0.01$), 4 ($p < 0.001$), 5, 6 and 7 ($p < 0.0001$). At day 7, the mean owner VAS pruritus score had reduced for the turmeric/black cumin treated dogs to 0.93 cm (a 6 cm reduction, which corresponds to a decrease from "severe itching" to "normal". The reduction in the owner VAS pruritus scores for placebo treated animals after 7 days was only 1.81 cm.

Veterinarian VAS dermatitis scores on each day of study

The mean day 0 veterinarian VAS dermatitis scores were similar ($p>0.05$) among the treatment groups (6.70 and 6.75 cm for turmeric/silymarin treated animals (range 2-10) and placebo control animals (range 2-10), separately. At day 7, mean veterinarian VAS dermatitis score for turmeric/black cumin treated animals declined to 1 cm (5.75 cm decrease from "moderately severe dermatitis" towards "normal"), the control animals to 5.2 cm (1.5 cm decrease from "moderately severe dermatitis" to "mildly moderate dermatitis") ($p<0.0001$). Veterinarian VAS dermatitis scores in the turmeric/silymarin treated animals were notably reduce compared to control dogs on day 7 ($p<0.0001$).

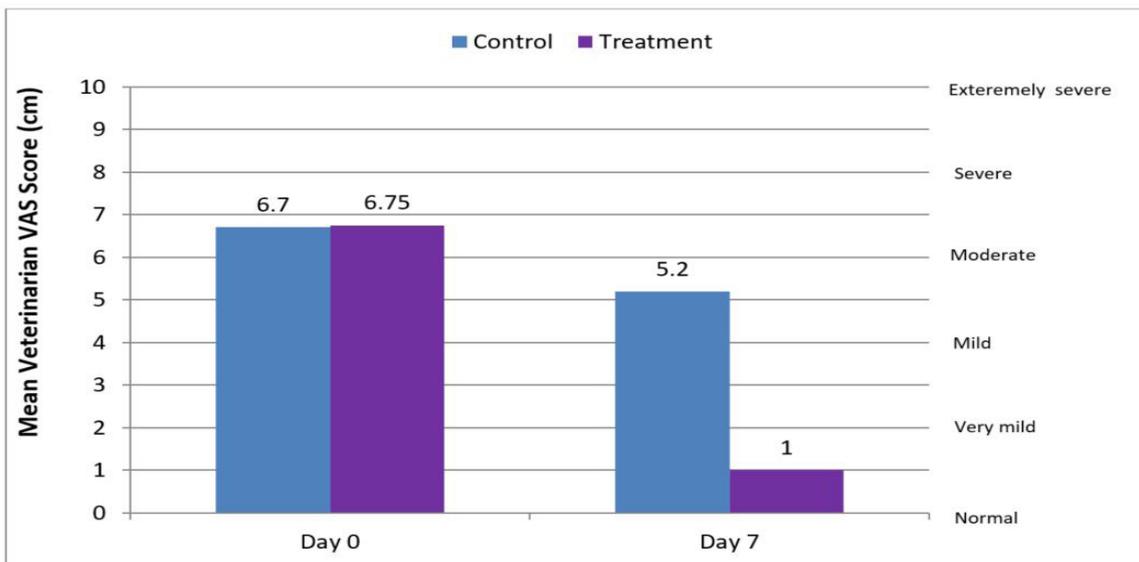


Figure 5. Mean veterinarian VAS scores throughout the study period.

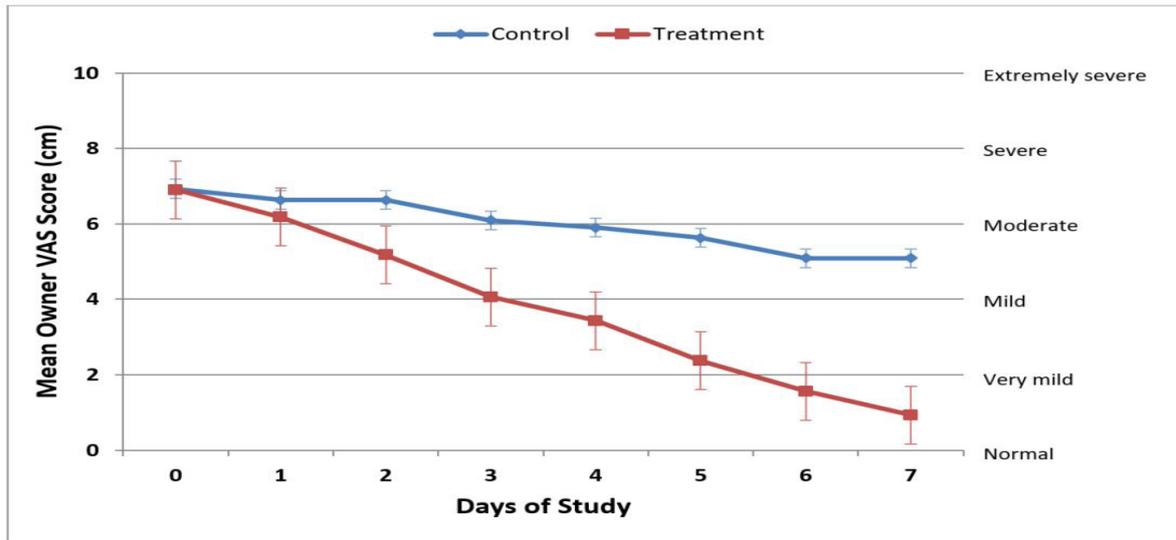


Figure 6. Mean owner VAS scores throughout the study period.

CADESI-04 analytes

Based on Hill's atopy index application by use of a iPhone 8 plus device scores ranged from 11 (mild Ad) to 126 (severe Ad), which were switched to 10- 99 after Silp treatment.

DISCUSSION

The results of the present study might be comparable to a prior research investigating the efficacy of oclacitinib (ocl) against pruritus to those of dogs with allergic dermatitis. In that study after 1 week of ocl treatment, a 65% decrement among pruritus scores (changed from 'severe to very mild itching'). Within the first day of ocl therapy, pruritus scores declined by at least 2 cm (44%) compared to those of the control-treated animals (19%). On week 1, the vast majority of the ocl-treated dogs (86.4%) presented a 2 cm decline in Owner Pruritus VAS scores when compared to placebo-treated dogs (<42.5%). Furthermore, on week 1, 70.5% of ocl-treated animals represented a >50% decline in Owner Pruritus VAS scores in contrast to <23.2% of the placebo cases. In the latter study ocl therapy resulted in treatment success (66.5% in ocl-treated vs. 29.4% of the placebo), making ocl improving pruritus and dermatitis (7). In comparison in the present study mean 0. day owner VAS pruritus scores were similar ($p>0.05$) between the treatment groups (6.90 and 6.93 cm for the Silp treated dogs (range 2-10) and control dogs (range 2-10), respectively. After 1 day of Silp treatment, a 0.55 cm decrement of mean owner VAS pruritus scores was detected in treatment group, while the control dogs had a 0.27 cm reduction. The mean owner VAS pruritus scores persistent to gradually reduce over other 6 days of study in the treatment group ($p<0.0001$). The mean owner VAS pruritus scores in the Silp treated dogs were notably lower compared to control treated dogs on days 3 ($P<0.01$), 4 ($p<0.001$), 5, 6 and 7 ($p<0.0001$). At day 7, the mean owner VAS pruritus score had reduced for the Silp treated animals to 0.93 cm (a 6 cm decrement, which means a decrease from "severe itching" to "normal". The decrease in owner VAS pruritus scores for control treated animals after 7 days was only 1.81 cm.

Instant depression (probably) of the activity of pruritogenic cytokines [i.e. Interleukin-31], might briefly define the quick decline in pruritus thereafter ocl therapy (8). Hence by management of the pruritus in dogs, a direct anti-inflammatory action might also occur within the dermis. Similarly in the present study a better understanding for the Silp treatment option could be available with the expression of the compound ingredients. Turmeric has a well-known interaction with several molecular targets participating within inflammation (9). The latter spice, reduce the amplitude of the inflammatory respond by down-regulating the activities of cyclooxygenase-2, lipoxygenase and nitric oxide synthase (9). Anti-inflammatory effects of curcumin might be dedicated to downregulation of the expression of TNF- α , cyclin D and cell surface adhesion molecules (10). In addition inhibition the activity of protein serine/threonine kinases, c-Jun N-terminal kinase and protein tyrosine kinase, might participate (11). From another point of view curcumin selectively inhibits phosphorylase kinase (12), the enzyme participate for breaking down glycogen, for formation of ATP, with a significant role for phosphorylation (13). The latter enzyme may be released only 300 seconds after injury, activating inflammatory cells (13-15), wound healing and scar tissue formation (16). Given the efficacy of curcumin able to inhibit phosphorylase kinase activity might have the potential for modulation of the inflammatory respond for influencing above mentioned factors. In the present study the oral compound used involved curcumin, in which supported the decreased VAS scales and related scoring by probable antiinflammatory action as reported previously and explored from human studies (8-16).

In the present study interpretation of pruritus was based on VAS scales, as was also reported and determined previously (7). In that research enhanced VAS scales were presented as an easy and quotable technique for practioners for assessing the severity of pruritus (20,22). In previous researches, a VAS scale was preferred for assessment of itching (23). Indeed, dogs may not truly present itching behaviour on referral. Thus scientists or practioners pruritus VAS score might have to lean on what the patient's owner report rather than observation

(7). On the other hand regarding Canine Atopic Dermatitis and Severity Index (CADESI), has long been known as an objective and validated assessment tools with limited usage confined now to atopic dermatitis, and might not be suitable for assessing the degree of the skin disorders (7), observed in this study. Enhanced dermatitis VAS used and adopted previously (7), which also adopted in the present study might have been useful for free veterinary surgeons participating at special practice with no special education nor certification in veterinary dermatology (7).

Berardesca *et al.* (17) denoted that silymarin along with methylsulfonylmethane were found effective for relieving pruritus and relevant clinical signs at erythematotelangiectatic phase of rosacea subtype-1. On the other hand topical silymarin diminished atopic dermatitis by suppression of mast cell infiltration in mice skin (18). Hence silymarin was able to reduce plasma IL-4 and IgE levels to those of mice. It has been postulated that silymarin be helpful for atopic dermatitis treatment (18). Mady *et al.* (19) used specific silymarin formulation significantly diminished redness, swelling, and inflammation in atopic dermatitis. All those aforementioned mechanisms might be possibly interact with the anti-pruritic armamentarium obtained in this study.

CONCLUSION

In conclusion it may be suggested that, curcumin, a selective Janus kinase inhibitor, prescribed per twice daily, along with silymarin, were both safe and effective for relieving pruritus in association with allergy in dogs. This natural (herbal in origin) compounds offered itch relief within 24 hours as was observed throughout study period, with the vast majority of treated animals presented a 5.75 cm decrease on pruritus (from “moderately severe dermatitis” to “normal”) by day 7. It should not be unwise to draw conclusion that this herbal compound might have helped pruritus relief and might be used with safety as an antipruritic agent.

DECLARATIONS

Ethics Approval

This study was approved by animal ethics committee of the Aydın Adnan Menderes University (No: 2019/022), Aydın.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contribution

Idea, concept and design: K Ural

Data collection and analysis: K Ural, M Gültekin, S Erdoğan, H Erdoğan

Drafting of the manuscript: K Ural, M Gültekin, S Erdoğan, H Erdoğan

Critical review: K Ural, M Gültekin, S Erdoğan, H Erdoğan

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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