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Evaluation of the efficacy and Safety of Palmitoylethanolamide (PEA) combination in managing dermatitis in dogs

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Abstract

Dermatitis is a common inflammatory skin condition in dogs, caused by allergies, infections, or autoimmune responses, leading to significant discomfort and reduced quality of life (QoL). This study evaluated the effectiveness and safety of Palmitoylethanolamide (PEA) combination-PEA 300mg + Daidzein 50mg + Genistein 4mg -in 18 dogs suffering from dermatitis. Dogs received PEA Combination twice daily for 28 days and were assessed on day 0 (baseline), 07, 14, 21 and 28 (End of study). Key evaluations included Canine Atopic Dermatitis Extent and Severity Index-4 (CADESI-4) and owner-reported QoL. CADESI-4 reduced significantly from 52.27±5.51 to 3.83±2.89 ($p<0.001$). QoL score significantly improved from 13.33±2.11 to 0.61±0.97 ($p<0.001$), while family concern scores improved from 5.55±1.33 to 0.22±0.42. Two cases of vomiting were reported as adverse events. The study concluded that PEA combination significantly reduced dermatitis and improved QoL in dogs, demonstrating safety and tolerability with no major adverse event.

Keywords: Dermatitis, Palmitoylethanolamide, CADESI-4, Quality of Life

Introduction

The ectoparasitic infestation in livestock and companion animal pose a major threat to the economy of the livestock and pet sector. Ticks are blood-sucking acarines whose survival and reproduction completely relies on the host existence. The losses incurred due to tick infestations not only include anaemia, hypersensitivity reactions, eczema, weight loss tick paralysis and tick toxicosis^[4] but also due to the wide ambit of diseases they transmit. Among the ticks infesting dogs, the kennel tick, *Rhipicephalus sanguineus* is cosmopolitan in distribution. They have been known to transmit protozoan parasites like *Babesia vogeli*, *B. gibsoni*, *Babesia canis* and *Hepatozoon canis*^[10], rickettsial parasites such as *Ehrlichia canis*, *Anaplasma platys*, *Rickettsia rickettsia* and *R. conorii*. The ticks thus gain veterinary significance especially due to their vectoral potency. Thus, an effective, sustained and plausible tick control measure has to be implemented in order to safeguard the health of pet animals.

Canine Atopic Dermatitis (CAD) is an inflammatory condition susceptible to genetics and itching skin disease due to allergy with typical medical features (Halliwell R, 2006; Drechsler Y, *et al.*, 2024)^[1, 2]. It is associated most commonly with IgE antibodies to environmental allergens (Halliwell R, 2006)^[1]. It affects up to 30% of dogs, causing severe itching and skin problems. Additionally, it leads to secondary infections, further complicating the treatment (Fernandes B, *et al.*, 2023)^[3]. The moderate to severe pruritus is the most common and clinically significant feature of CAD, which is accompanied by, and typically precedes, erythema, erythematous macular and/or papular eruptions, self-induced alopecia, excoriations, hyperpigmentation, and lichenification (Bizikova P, *et al.*, 2015; Hensel P, *et al.*, 2015; Favrot C, *et al.*, 2010)^[4-6]. In different breeds of the dogs, the distribution of skin lesions varies, but mostly involves the face, pinnae, ear canals, paws, axillae, ventrum, and inguinum (Bizikova P, *et al.*, 2015; Hensel P, *et al.*, 2015; Favrot C, *et al.*, 2010; Wilhem S, *et al.*, 2011)^[4-7].

Before the age of 3 years, the clinical signs of CAD starts appearing and it may be either perennial or seasonal, and overlap with numerous other pruritic and inflammatory skin diseases (Bizikova P, *et al.*, 2015) ^[4]. However, there is no definitive diagnostic test or pathognomonic clinical sign that can be used to make a diagnosis of CAD.

The development of Canine atopic dermatitis (CAD) involves the interaction between genetic and environmental factors (Marsella R, 2021) ^[8]. These factors can influence the immune response, the skin microbiome and the integumentary barrier, resulting in the synthesis of pro-inflammatory molecules that potentially perpetuate and aggravate skin inflammation (Stefanovic N, *et al.*, 2021) ^[9].

The pruritus is a symbolic clinical sign of CAD and is often the main presenting complaint when owners of dogs with CAD seek veterinary care. Providing immediate and sustained anti-itch relief is a primary therapeutic goal in managing CAD. For managing CAD, the right combination of therapies for each individual dog is very important because that will provide a safe, effective and affordable management strategy that the respective pet owner can reliably and willingly execute (Outerbridge CA and Jordan TJ, 2021) ^[10]. The treatment of choice for CAD is aqueous immunotherapy, which seems to be 60-85% effective in controlling clinical signs in cases with nonseasonal disease (Griffin CE and Hillier A, 2001) ^[11]. Other palliative treatments for CAD traditionally involve the use of glucocorticoids and calcineurin inhibitors, both topically and systemically. Oral cyclosporine has been shown to be as effective as glucocorticoids (Steffan, *et al.*, 2006) ^[12] and is reserved for cases that have failed other forms of therapy; topical tacrolimus is very effective in individuals with localized disease (Marsella, *et al.*, 2004) ^[13]. Further, Antihistamines, topical antipruritic agents are also available for the treatment of CAD (Drechsler Y, *et al.*, 2024) ^[2]. However, with these treatment agents, the chances of side effects are more. Hence, the effective and well tolerable pharmacotherapy is required for the management of CAD.

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide with anti-inflammatory and analgesic properties (Clayton P, *et al.*, 2021) ^[14]. Previous studies concluded that PEA appears to be effective and safe in reducing pruritus and skin lesions, and in improving QoL in dogs with moderate atopic dermatitis and moderate pruritus (Noli C, *et al.*, 2015) ^[15]. PEA has emerged as a disease-modifying agent in conditions eliciting both inflammatory and neuropathic pain, both in experimental (e.g. intraplantar injection of formalin, chronic constriction injury, viscerovisceral hyperalgesia) and naturally occurring conditions (e.g. diabetic neuropathy, low back pain and pelvic pain in human patients), (Re G, *et al.*, 2007; Petrosino and Di Marzo, 2017; Skaper, *et al.*, 2014) ^[16-18]. Considering the PEA's effect in managing the atopic dermatitis, the current study investigated the efficacy, safety and tolerability of PEA in combination with the Daidzein and Genistein for reducing the dermatitis and improving the quality of life scores in dogs.

Materials and Methods

This study enrolled 18 Labrador breed of dogs. Among them, 12 were males, and six were females who were neither pregnant nor lactating. All the dogs were aged 2 to 10 years and diagnosed with the dermatitis. Dogs with either seasonal pruritus or concurrent illnesses such as bacterial pyoderma,

Malassezia dermatitis, or ectoparasite infestation were not included in the study. Dogs with malnourishment, known allergies to PEA combination, severe systemic diseases or currently participating in another pre-clinical trial were excluded during the screening. Mean age and height of the dogs were 4.27 ± 1.56 yrs. and 57.22 ± 3.45 cm, respectively at baseline. The study adhered strictly to ethical guidelines for veterinary research. Prior to enrolment, informed consent was received from the pet owners, ensuring ethical compliance. The trial was conducted with the utmost regard for animal welfare.

The trial was completed within a time of 28 days, with assessment on baseline visit 1 (Day 0), visit 2 (Day 07), visit 3 (Day 14), visit 4 (Day 21), and EOS visit 5 (Day 28). The primary endpoint was the assessment of reduction in dermatitis symptoms using a standardized dermatitis scoring system. The secondary endpoints included incidences of adverse events, changes in quality-of-life scores and owner-reported outcomes during the study course. The dogs underwent physical examination, including weight, temperature, heart rate and respiratory rate at each study visit. The body condition scores (BCS) as well as extent and severity of dermatitis assessed by CADESI-4 score, were recorded at each visit, whereas QoL score were measured at baseline visit (Day 0), and EOS visit (Day 28). The animals received the test treatment of PEA combination i.e. PEA 300 mg + Daidzein 50 mg + Genistein 4 mg orally along with water twice daily for 28 days, with an extra 2-days buffer to allow any scheduling changes. As a part of initial assessment at baseline visit on Day 0, a general evaluation of the dog's health including detailed medical history review, physical examination and BCS was performed. After baseline assessment of CADESI-4 score, QoL score was also evaluated to provide a holistic view of dog's well-being before treatment initiation. PEA combination tablets were dispensed. Considering the single-arm, open-label study, all the animals were treated with the same test formulation.

The dogs were provided with free access to food and water, and their diet remained consistent throughout the study to eliminate any potential confounding factors. The administration of PEA combination continued uninterrupted through Day 28. The trial was conducted to assess the effectiveness and safety of PEA combination in managing dermatitis in dogs. The dogs were recruited from the veterinary centers and hospitals and identified from owners who provided informed consent experiencing dermatitis.

Body Condition Scores (BCS)

Body condition scores was having a scale of score 1 to 9. BCS such as 1 to 3 represented under ideal body condition, 4 and 5 represented ideal body condition and 6 to 9 represented over ideal body condition. BCS 6 and 7 interpreted as a bit over ideal body condition (wsava.org, 2013) ^[19]. The figure of BCS is presented below as Figure 1.

Food and Nutrition status

The food and nutrition status were performed on baseline visit only. Dogs' food was categorized as homemade (5), commercial (4), and homemade + commercial both (9). The feeding schedule for 11 out of 18 dogs was twice daily, while the seven dogs were used to have food thrice daily. Only eight dogs were used to have supplements, while 10 dogs were without supplements.

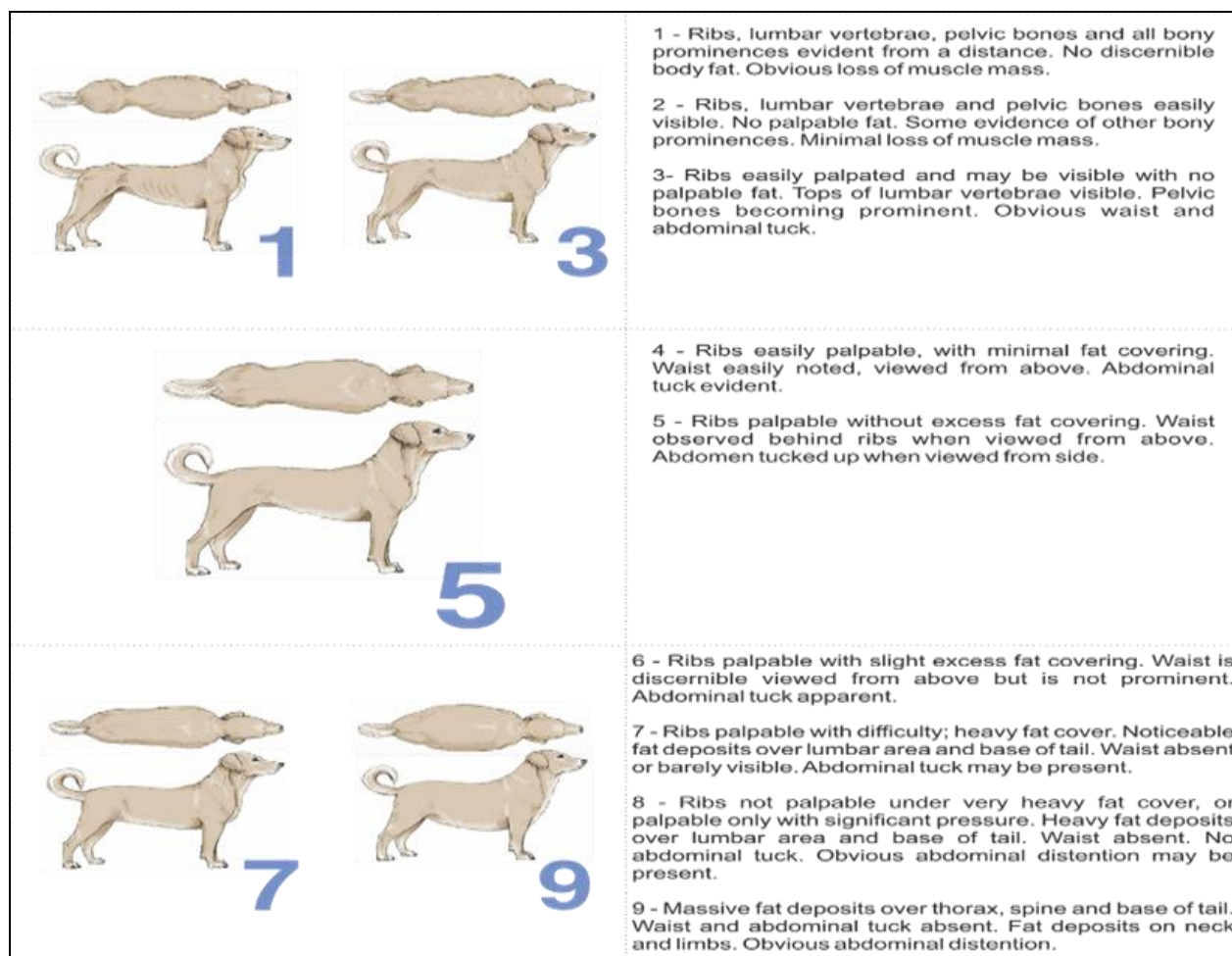


Fig 1: Body Condition Score

Canine atopic dermatitis extent and severity index-4 (CADESI-4)

The CADESI-4 was used as a tool to determine the score of dermatitis in terms of extent and severity. The CADESI-4 was designed to comprise 20 body sites and three lesions (Erythema, Lichenification and Excoriations and/or Alopecia). There were four severity grades starting from 0=none, 1=mild, 2=moderate and 3=severe. Each site and

each lesion type was given a score from 0 to 3 depending on the severity and extent of the dermatitis. Considering three lesions and four severity grades, a maximal score of $20 \times 3 \times 3 = 180$ could be given. The body sites evaluated in the CADESI-4 are shown in Figure 2 (Olivry T, *et al.*, 2014) [20]. CADESI-4 scoring form is shown in Figure 3 (Dryden MW, *et al.*, 2016) [21].

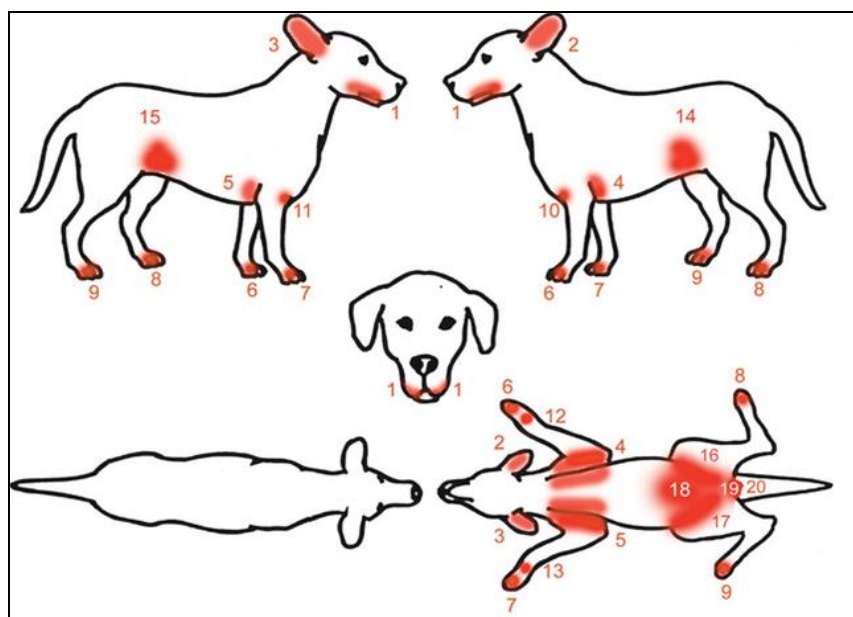


Fig 2: Body sites evaluated in CADESI-4

			Erythema	Lichenification	Excoriations and/or Alopecia	Total
Perilabial Area (left & Right Combined)		1				
Medial Pinnae (Concave Pinnae)	Left	2				
	Right	3				
Axillae	Left	4				
	Right	5				
Front Paws (dorsal and Palmar Side Combined)	Left	6				
	Right	7				
Hind Paws (dorsal and Palmar Side Combined)	Left	8				
	Right	9				
Cubital Flexor (Elbow Folds)	Left	10				
	Right	11				
Palmar Metacarpal (from Carpal to Metacarpal Pads)	Left	12				
	Right	13				
Flanks	Left	14				
	Right	15				
Inguinal Areas (groin)	Left	16				
	Right	17				
Abdomen		18				
Perineum (from vulva/scrotum to anus)		19				
Ventral Tail (proximal)		20				
Grade each site and each lesion type None:0, Mild:1, Moderate:2, Severe:3			Total score (20X3X3=180)			

Fig 3: CADESI-4 scoring form

Quality of Life Score (QoL)

The overall pet's QoL score was used as a parameter of pet's medical condition and family's concern. The pet's QoL score was calculated based on the total of 16 aspects of medical condition including the social function, natural function, mental health and physical health. Each aspect was scored from 0 to 2; where score 0 indicated "I agree with statement", score 1 indicated "see some changes" and score 2 indicated "I disagree with statement". The result of QoL was interpreted as per the total QoL score. The total QoL scores 0 to 8 indicated "Most likely adequate", 9 to 16 indicated "questionable and medical intervention is suggested" and 17 to 36 indicated "definite concern" (McVety) ^[22].

The family's concern was assessed using eight specific concerns. Each concern was given a score from 0 to 2; where score 0 indicated "I am not concerned at this time", score 1 indicated "There is some concern" and score 2 indicated "I am concerned about this". The result of family's concern was interpreted as per the total family's concern score. The total family's concern scores 0 to 4 indicated "Minimal concern", 5 to 9 indicated "Concerns are mounting" and 10 to 16 indicated "Valid concerns" (McVety) ^[22].

Statistical Analysis

Descriptive statistics and comparative statistical tests were

conducted for evaluating the efficacy and safety of PEA combination in managing dermatitis in dogs. Descriptive statistics summarized the dermatitis scores using measures such as mean and standard deviation to provide an overview of the data distribution before and after the treatment. To assess the effectiveness of PEA combination, dermatitis scores pre and post treatment period were compared using a paired t-test to analyze the mean dermatitis scores change.

Results

The study assessed the effects of PEA combination tablets administered orally to dogs suffering due to diseased skin condition i.e. dermatitis. Demographic, BCS, food and nutrition, physical examination, CADESI-4 and QoL score details were collected at baseline visit along with blood tests to examine health status.

Findings of Physical Examination

The result of the physical examination is summarized in Tables 1. The dogs' weight, temperature, heart rate and respiratory rate were recorded at each visit. All parameters were in normal range throughout the study period. No noticeable finding was observed in any physical examination parameter at day 7, 14, 21 and day 28 compared to baseline.

Table 1: The Summary of the change in Physical Examination

Parameter	Day 0 (Baseline)	Day 7	Day 14	Day 21	Day 28 (EOS)
Weight (kg)	33.66 ± 3.28	33.70 ± 3.23	33.58 ± 3.18	33.62 ± 3.26	33.68 ± 3.31
Temperature (F)	101.85 ± 0.47	101.82 ± 0.50	101.51 ± 0.42	101.65 ± 0.50	101.71 ± 0.44
Heart Rate (Beats/Min)	74.83 ± 9.46	75.5 ± 10.25	77.66 ± 9.50	75.61 ± 9.57	77.66 ± 8.57
Respiratory Rate (Breaths/Min)	15.11 ± 2.58	14.44 ± 2.99	15.00 ± 2.72	14.83 ± 2.38	15.72 ± 2.56

Data are presented as Mean ± SD.

Results of Body Condition Score (BCS)

The pets' body condition were categorized based on scale of the body condition score. The BCS 3 considered as "Below Ideal Condition", 4 and 5 are considered as "Ideal Body Condition", 6 and 7 are considered as "Over Ideal Condition". The result of the body condition score is summarized in Table

3. At baseline, no dogs were below-ideal body condition, 15 dogs were in ideal body condition, and three dogs were over ideal body condition. BCS was recorded on Day 7, 14, 21 and 28. The results have shown that at EOS, 14 dogs remained in ideal body condition, while 4 dogs were over ideal body condition.

Table 3: Summary of the change in BCS

Body Condition Score		Day 0 (Baseline), (N)	Day 7, (N)	Day 14, (N)	Day 21, (N)	Day 28 (EOS), (N)
Ideal Body Condition	4	9	9	9	9	9
	5	6	6	7	5	5
Over Ideal Condition	6	2	2	1	3	3
	7	1	1	1	1	1

N=Number of participated dogs in specified category

Results of Canine Atopic Dermatitis Extent and Severity Index-4 (CADESI-4)

The result of Canine Atopic Dermatitis Extent and Severity Index-4 is summarized in Table 4. At baseline, the dogs were suffering from severe and significant dermatitis. The CADESI-4 score was 52.27 ± 5.51 at baseline (Day 0), which was reduced to 39.83 ± 4.79 by Day 7, 24.94 ± 3.93 by Day 14,

10.72 ± 2.96 by Day 21 and 3.83 ± 2.89 by EOS (Day 28). The statistically significant reduction (with a p-value of < 0.001) was observed in extent and severity of the dermatitis from baseline to EOS indicating marked improvement in dermatitis with the treatment of PEA combination in the dogs. The dermatitis skin condition before treatment and post treatment are shown in Figure 4 and 5, respectively.

Table 4: Summary of change CADESI-4

		Day 0 (Baseline)	Day 7	Day 14	Day 21	Day 28 (EOS)	Change from Baseline to day 28
Score		52.27 ± 5.51	39.83 ± 4.79	24.94 ± 3.93	10.72 ± 2.96	3.83 ± 2.89	-48.44 ± 2.62
P-Value		-	-	-	-	-	< 0.001

Data are presented as Mean $\pm$ SD.



Fig 4: Dermatitis skin condition before treatment

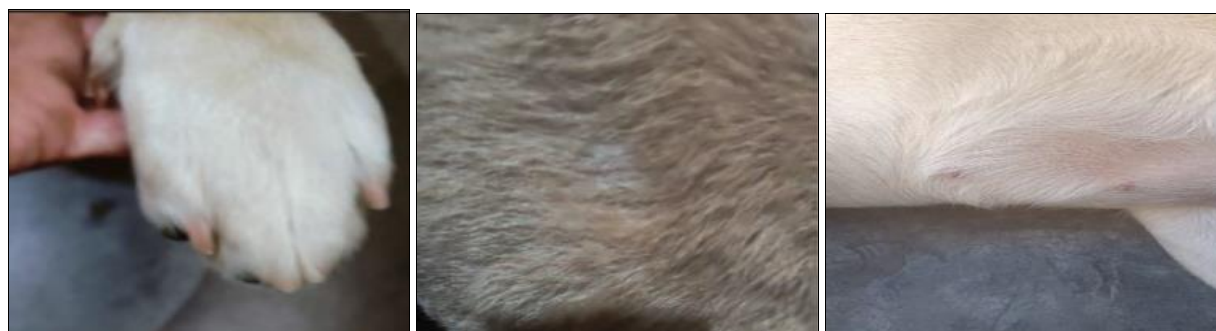


Fig 5: Post-Treatment skin condition of enrolled dogs

Results of Quality of Life Score

The result of the Quality of Life Score is summarized in Table 5. The mean Pet's QoL score at baseline was 13.33 ± 2.11 , representing a definite concern and the need for veterinary guidance. This score was reduced to 0.61 ± 0.97 by EOS. It was statistically significant difference (with a p-value of < 0.001) in QoL between pre and post treatment with the PEA combination in the dogs, indicating adequate QoL. Along

with QoL score, family concern for the pets was also taken into consideration as one the measure. The mean Family Concern score at baseline was 5.55 ± 1.33 , indicating that family/pet owner concerns about their pet were valid. This score was markedly reduced to 0.22 ± 0.42 (with a p-value of < 0.001) by EOS, indicating minimal concerns of the family towards the pet's health. The positive change in quality of life of the pets as well as the improvement in family concern

about their pets after the PEA combination treatment was statistically significant.

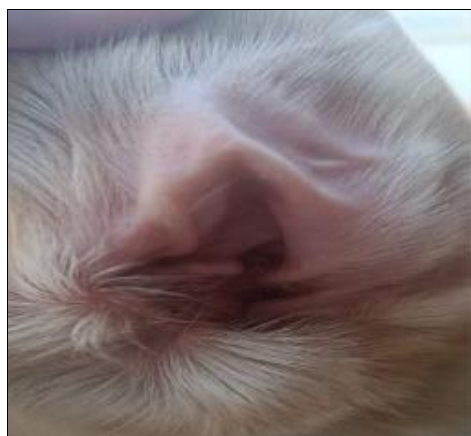
Table 5: Summary of change in the Quality of Life (QoL)

Quality of Life		Day 0 (Baseline)	Day 28 (EOS)
QoL Score		13.33±2.11	0.61±0.97
	P-Value	-	< 0.001
Family's Concerns		5.55±1.33	0.22±0.42
	P-Value	-	< 0.001

Data are presented as Mean ± SD

Safety Results

Two cases of vomiting were reported as adverse events during the study conduct.



Discussion

Dermatitis is a disease condition of the skin with increasing and relapsing itching and inflammation. The clinical signs of dermatitis is related to immunoglobulin (Ig) E antibodies. Dermatitis affects the quality of life of the pets in such a way that it needs permanent treatment many times (Outerbridge CA and Jordan TJ, 2021) [10]. The diagnosis of CAD is based upon clinical history, physical examination, characteristic clinical features with exclusion of other diseases with a similar clinical presentation and diagnostic tests including allergen-specific IgE serology (ASigES). Atopic dermatitis is usually a life-long disease that can be controlled but rarely cured (Brar RK *et al.*, 2017) [23]. In this study, dermatitis was measured using CADESI-4 as a primary endpoint and the adverse events, quality of life and owner reported outcomes as a secondary endpoint.

Palmitoylethanolamide (PEA) is a naturally occurring bioactive lipid compound and an endocannabinoid like molecule. PEA mechanism of action includes inhibition of inflammatory mediators, reduction of itching and pain, improvement of skin barrier function (Cerrato S, *et al.*, 2010) [24]. Considering the effectiveness of PEA combination, the present study aimed to evaluate its efficacy and safety in the dogs suffering from dermatitis.

The physical examination was conducted at every visit to evaluate any change in physical parameters due to PEA combination. From baseline to end of study, all physical parameters were normal indicating all the dogs were in healthy condition, thereby inferring that the PEA combination is having no any harmful effects on functioning of body system.

Similarly, the assessment of body condition score was performed on every visit to evaluate the changes in body

condition score. The body condition score of mostly all the dogs remained same at the EOS as compare to baseline except one dog whose body condition score was changed from ideal body condition to over ideal body condition.

There were various studies of PEA in some allergic condition, pruritus and skin lesions in pet animals. In one study conducted on canine skin mast cells, PEA (in doses ranging from 10^{-8} M to 10^{-5} M) induced a significant and dose-dependent inhibition of PGD₂, TNF- α and histamine release (Cerrato S, *et al.*, 2010) [24]. In *Ascaris* hypersensitive beagle dogs, a single oral dose of um-PEA (at doses of 3, 10 and 30 mg/kg) significantly reduced allergic wheal reactions in skin (Cerrato S, *et al.*, 2012) [25]. Treatment with PEA also showed improvement of clinical signs in cats with eosinophilic granuloma (Scarampella F, *et al.*, 2001) [26]. Another study showed that treatment with PEA was effective in the improvement of skin lesions and pruritus in dogs with atopic dermatitis and moderate pruritus (Noli C, *et al.*, 2015) [15]. Similar to all these study results, PEA combination has shown its effectiveness in dermatitis in dogs. On receiving PEA combination treatment, the CADESI-4 scoring was started reducing gradually. PEA combination showed significant reduction in CADESI-4 (reduction by -48.44 points, $p < 0.001$) at the end of study with comparison to the baseline indicating an improvement in dogs' dermatitis condition. The findings demonstrated the effectiveness of PEA combination, in treating dermatitis in dogs by reducing its extent as well as its severity.

The treatment with PEA combination showed an improvement in the level of quality of life in the dogs, with the significant improvement seen at Day 28 with comparison to Day 0. The significant reduction in QoL score from 13.33 on Day 0 to 0.61 on Day 28 (reduction by -12.72 points, $p < 0.001$), is indicating that the quality of living was improved evidently. Similar to QoL score, family's concern score was also reduced at significant level from 5.55 on Day 0 to 0.22 on Day 28 (reduction by -5.33 points, $p < 0.001$) indicating a noticeable improvement in the family's concern.

The treatment of PEA combination twice daily for 28 days, resulted into the occurrence of two AEs of vomiting without any major severity indicating that the PEA combination is very safe and easily tolerable by the dogs in given dosage.

Conclusion

This study concluded that the PEA combination significantly reduced extent and severity of dermatitis and improved quality of life scores in dogs. PEA combination also demonstrated to be safe and tolerable as no major adverse event was occurred during the study course.

Conflict of Interest

The authors declare that there is no conflict of interest.

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