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Evaluation of the efficacy and safety of Palmitoylethanolamide (PEA) combination in managing the pain in dogs

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Abstract

Chronic pain significantly affects quality of life (QoL) and behaviour in dogs. This study evaluated the efficacy and safety of a Palmitoylethanolamide (PEA) combination (PEA 300 mg + Daidzein 50 mg + Genistein 4 mg) administered twice daily for 28 days in 12 dogs with chronic pain. Assessments were conducted on Day 0 (baseline), Day 14, and Day 28 (end of study, EOS), including physical exams, Canine Brief Pain Inventory (CBPI), and owner-reported QoL scores. Results showed marked improvement by EOS: Pain Severity Score decreased from 27.58 ± 2.74 to 16.41 ± 2.60 , Pain Interference Score from 47.66 ± 2.99 to 27.41 ± 2.96 , and total CBPI score from 75.25 ± 5.73 to 43.83 ± 5.56 . QoL scores improved from 21.41 ± 2.77 to 7.58 ± 1.56 , and Family Concern score from 10.08 ± 2.15 to 3.50 ± 1.44 . Three mild adverse events (two cases of vomiting, one case of fever) were reported. The study concludes that the PEA combination is effective, safe, and well tolerated in managing chronic pain in dogs.

Keywords: Palmitoylethanolamide, pain, canine brief pain inventory, quality of life

Introduction

Pain is defined as “A kind of unpleasurable physical and emotional feeling related to real or possible tissue destruction, or termed as such harm (Valverde A *et al.*, 2005) ^[1]. Pain is of three types depending on its duration i.e. acute, chronic and intermittent and is categorized as mild, moderate, severe and excruciating depending on its severity (Belshaw Z *et al.*, 2018) ^[2]. Chronic pain typically refers to pain lasted for greater than three months to less than six months. The inciting cause may or may not be present (Walsh K, 2016) ^[3]. The chronic pain may lead to changes in the brain, which affects mental function and emotional condition, leads to reduced Quality of Life (QoL), (Christiansen S *et al.*, 2024, Mota-Rojas D *et al.*, 2022) ^[4, 5]. It affects life of dogs with reported signs including decreased movement, variation in hunger, less peaceful sleep and alteration of sleeping posture, change in the deportment and deviation in walking style that may include rigidity or lameness (Malkani R *et al.*, 2024) ^[6]. It is very important to discuss the aim of the treatment plan as pet's quality of life and the duration of treatment, both are major concerns (Walsh K, 2016) ^[3]. The treatment modalities for pain generally involves the use of various medications including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, local anesthetics etc. Other drugs like anti-histaminics, α 2-agonists, ketamine and gabapentin can also be used. Along with these medicines, acupuncture, physiotherapy etc. can be useful in reducing the pain (Viñuela-Fernández I *et al.*, 2007) ^[7]. While these medications can provide significant pain relief, they may cause gastrointestinal problems, liver and kidney damage (Luna SP *et al.*, 2007) ^[8]. Considering this scenario, the Palmitoylethanolamide (PEA) is a favorable choice, as it originates from food sources and animal tissues as N-acyl ethanolamine. For pet animals, it is used in some foods as highly absorbable micronized preparations (Della Rocca G *et al.*, 2021) ^[9].

PEA acts like a disease-modifying drug to treat inflammation and neuropathic pain (Re G *et al.*, 2007, Petrosino S *et al.*, 2017, Skaper SD *et al.*, 2014) ^[10, 11, 12]. Furthermore, PEA is now-a-days known as a negative inflammatory controller.

Furthermore, PEA is now-a-days known as a negative inflammatory controller (Petrosino S *et al.*, 2017, Solorzano C *et al.*, 2009) ^[11, 13]. Considering the PEA's effect in managing the pain, the current study investigated the efficacy, safety and tolerability of PEA in combination with the Daidzein and Genistein for reducing the pain and improving the quality of life scores in dogs.

Materials and Methods

This study included 12 dogs of various breeds that included Labrador (three), German shepherd (five), Beagle (three), and Golden Retriever (one). Among them, seven were males, and five were females who were neither pregnant nor nursing. All the dogs were aged 10 and above and diagnosed with the chronic pain conditions, defined as persistent pain lasting more than three months. Dogs with known allergies to PEA combination, severe systemic diseases or currently participating in another pre-clinical trial were excluded during the screening. Mean age, weight and height of the dogs were 10.66±0.77 years, 30.72±13.62 kg and 53.33±10.69 cm respectively at baseline. The study adhered strictly to ethical guidelines for veterinary and as per the general research principles. Prior to enrolment, informed consent was obtained from the owners, ensuring ethical compliance.

The total study duration was of 28 days, including the assessments scheduled at baseline visit 1 (Day 0), visit 2 (Day 14), and at EOS visit 3 (Day 28). The primary endpoint was the assessment of reduction in pain with the help of the Canine Brief Pain Inventory (CBPI), and reduction observed in the Pain Severity Score (PSS) and the Pain Interference Score (PIS). The secondary end-points were any adverse events, changes in quality-of-life scores and owner-reported outcomes during the study course. The dogs were undergone physical examination including the recording of weight, temperature, heart rate and respiratory rate at each visit. The Body Condition Scores (BCS) was performed on each visit, whereas CBPI and QoL score were measured at baseline visit (Day 0), visit 2 (Day 14) 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 vital signs measurement, BCS, medical history of any illness or allergy, body weight measurement was performed. The laboratory examination including blood tests i.e. CBC and serum biochemistry were performed for all dogs during the baseline visit. In this trial, effectiveness of PEA combination in managing chronic pain in dogs was evaluated. The dogs were recruited from the veterinary clinics and hospitals and identified from owners who provided informed consent experiencing from chronic pain.

Body Condition Scores (BCS)

Body condition scores was having a scale of score one to nine. BCS such as one to three represented under ideal body condition, four and five represented ideal body condition and

six to nine represented over ideal body condition. As per the scale of BCS, score three can be interpreted as a bit under ideal body condition whereas the score six and seven can be interpreted as a bit over ideal body condition (Wsava.org, 2013) ^[14]. The figure of BCS is presented below.

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Food and Nutrition status

The food and nutrition status were performed on baseline visit only. Dogs' food was categorized as homemade (3), commercial (2), and both (7). The feeding schedule for 7 out of 12 dogs were twice daily, while the 5 dogs were used to have food thrice daily. Only 5 dogs were used to have supplements, while 7 dogs were without supplements.

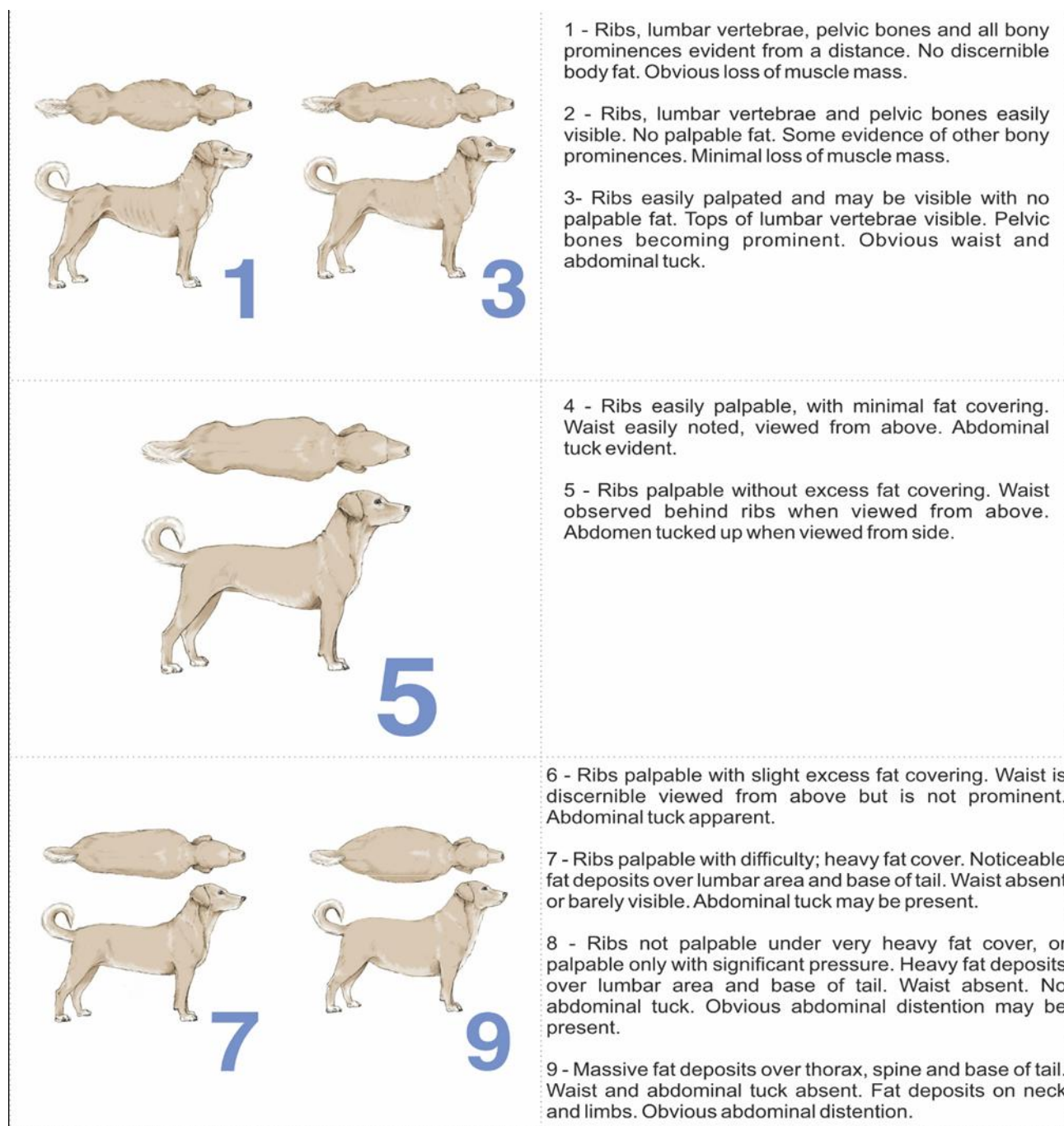
Canine Brief Pain Inventory (CBPI)

CBPI score involves two main factors: Pain Severity Score (PSS) and Pain Interference Score (PIS). CBPI score was based on the 11 questionnaires, mostly related to description of pain severity, interference of pain in routine function and overall impression. The scale of the pain severity score was having a range of 10 points i.e. from "No pain" with 0 score to "Extreme pain" with 10 score. Similarly, the scale of interference of pain in routine function was having a range of 10 points i.e. from "Does not interfere" with 0 score to "Completely interferes" with 10 score. The overall expression was determined by a scale of five-points i.e. from "Poor" to "Excellent".

Quality of Life Score (QoL)

The overall pet's QoL score was used as a parameter of pet's medical condition as well as 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 given a score from 0 to 2; where score 0 designated "I agree with statement", score 1 designated "see some changes" and score 2 designated "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, N.D.) ^[15].

The family's concern was calculated based on the eight concerns of the family member. 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, N.D.) ^[15].



Statistical Analysis

Descriptive statistics and comparative statistical tests were conducted to evaluate the efficacy and safety of PEA combination in managing chronic pain in dogs. To assess the effectiveness of PEA combination, pain scores pre and post-treatment period were compared using a paired t-test to analyze the mean pain scores (PSS and PIS) change.

Results

The study assessed the effects of oral administration of PEA combination tablets in dogs suffering with chronic pain. Demographic, body condition score, food and nutrition 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 site visit. All parameters were in normal range throughout the study period. No noticeable finding was observed in any physical examination parameter at day 14 and day 28 compared to baseline.

Table 1: The Summary of the change in Physical Examination

Physical Parameter	Day Zero (Baseline)	Day 14	Day 28 (EOS)
Weight (kg)	30.72±13.62	30.81±13.53	30.95±13.52
Temperature (F)	101.64±0.44	101.65±0.57	101.71±0.52
Heart Rate (Beats /Min)	90.00±21.22	89.5±25.77	91.41±31.55
Respiratory Rate (Breaths/Min)	17.83±4.38	17.41±5.16	17.33±4.81

Data are presented as Mean± SD. Data are presented as Mean± SD.

Laboratory Examination of Blood Test

The laboratory examination was performed at baseline visit and the report of blood parameters were found to be in normal

range. The blood tests showed a mean RBC count of $6.55 \pm 0.83 \times 10^6/\mu\text{L}$, a mean WBC count of $94.50 \pm 27.41/\mu\text{L}$ and mean platelets of $28.33 \pm 11.84/\mu\text{L}$. The liver function test and renal function test was also covered in blood test. The mean ALT was $68.91 \pm 12.56 \text{ U/L}$, AST was $24.33 \pm 8.22 \text{ U/L}$, and ALP was $66.16 \pm 11.18 \text{ U/L}$ whereas, the mean creatinine was $0.90 \pm 0.31 \text{ mg/dL}$, BUN was $16.66 \pm 4.07 \text{ mg/dL}$, and glucose was $87.75 \pm 9.62 \text{ mg/dL}$. Moreover, the level of electrolytes was also measured i.e. Sodium averaged $14.58 \pm 6.27 \text{ mmol/L}$, potassium was $4.48 \pm 0.63 \text{ mmol/L}$, and chloride was $10.30 \pm 4.49 \text{ mmol/L}$. Considering the normal blood report, the dogs were included for participating in the trial. The report of the blood test is also presented in tabular form in Table 2.

Table 2: The laboratory examination of blood parameters in dogs

Blood Parameters	Day 0 (Baseline)
RBC ($\times 10^6/\mu\text{L}$)	6.55 ± 0.83
WBC ($/\mu\text{L}$)	94.50 ± 27.41
Platelets ($/\mu\text{L}$)	28.33 ± 11.84
ALT (U/L)	68.91 ± 12.56
AST (U/L)	24.33 ± 8.22
ALP (U/L)	66.16 ± 11.18
Creatinine (mg/dL)	0.90 ± 0.31
BUN (mg/dL)	16.66 ± 4.07
Glucose (mg/dL)	87.75 ± 9.62
Sodium (mmol/L)	14.58 ± 6.27
Potassium (mmol/L)	4.48 ± 0.63
Chloride (mmol/L)	10.30 ± 4.49

Data are presented as Mean $\pm$ SD.

Results of Body Condition Score (BCS)

Based on a scale of body condition score, the pets of different body conditions are categorized. The score of 3 is reflected as "Below Ideal Condition", the score of 4 and 5 are considered as "Ideal Body Condition", whereas the score of 6 and 7 are considered as a bit "Over Ideal Condition". The result of the body condition score is summarized in Table 3. At baseline, one dog was categorized as having a below ideal body condition, and this status did not change by EOS on Day 28. Four dogs were assessed as over ideal body condition, and seven dogs had an ideal body condition score at baseline. The body condition score was also recorded on Day 14 as well as at EOS on Day 28. The results have shown that the BCS of all the dogs remained unchanged at Day 28.

Table 3: The summary of the change in BCS

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

N=Number of participated dogs in specified category

Results of Canine Brief Pain Inventory (CBPI)

The result of the CBPI score is summarized in Table 4. The total CBPI score consisted of PSS and PIS. At starting of the trial, the dogs were suffering from severe and significant chronic pain. The PSS was 27.58 ± 2.74 at baseline (Day 0), which was reduced to 22.66 ± 3.11 by Day 14 and 16.41 ± 2.60 by EOS on Day 28. There was statistically significant

difference (with a p -value of < 0.001) observed in severity of the pain between pre and post treatment with the PEA combination in the dogs suffering from chronic pain. The statistically significant reduction was also observed in PIS. The PIS was 47.66 ± 2.99 at baseline (Day 0), which was markedly decreased to 40.66 ± 2.49 by Day 14 and 27.41 ± 2.96 by EOS on Day 28, with a p -value of < 0.001 . It was noticed significant improvement in the pain interference in dogs after the PEA combination treatment. The Total CBPI score was calculated by summation of PSS and PIS. The total CBPI score was 75.25 ± 5.73 at baseline on Day 0 which was significantly reduced (with a p -value of < 0.001) to 63.33 ± 5.60 by Day 14 and 43.83 ± 5.56 at the EOS on Day 28.

Table 4: The summary of change in the CBPI

CBPI Scores		Day 0 (Baseline)	Day 14	Day 28 (EOS)
Pain Severity Score (PSS)		27.58 ± 2.74	22.66 ± 3.11	16.41 ± 2.60
	P-Value	-	< 0.001	< 0.001
Pain Interference Score (PIS)		47.66 ± 2.99	40.66 ± 2.49	27.41 ± 2.96
	P-Value	-	< 0.001	< 0.001
Total CBPI		75.25 ± 5.73	63.33 ± 5.60	43.83 ± 5.56
	P-Value	-	< 0.001	< 0.001

Data are presented as Mean $\pm$ SD

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 21.41 ± 2.77 , representing a definite concern and the need for veterinary guidance. This score was reduced to 15.91 ± 2.31 by Day 14 and 7.58 ± 1.56 by EOS on Day 28. 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 but still a need for veterinary guidance. 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 10.08 ± 2.15 , indicating that family/pet owner concerns about their pet were valid. This score was markedly reduced to 7.08 ± 1.50 by Day 14 and 3.50 ± 1.44 (with a p -value of < 0.001) by EOS on Day 28, 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: The summary of change in the QoL

QoL		Day 0 (Baseline)	Day 14	Day 28 (EOS)
QoL Score		21.41 ± 2.77	15.91 ± 2.31	7.58 ± 1.56
	P-Value	-	< 0.001	< 0.001
Family's Concerns		10.08 ± 2.15	7.08 ± 1.50	3.50 ± 1.44
	P-Value	-	< 0.001	< 0.001

Data are presented as Mean $\pm$ SD

Safety Results

A total of three adverse events (AEs) were observed during the conduct of the study, including two events of vomiting and one of fever.

Discussion

The long lasting pain can markedly disturb the health of any pet. The typical sign like illness related to muscle and

skeleton such as change in the walking style, rigidity in muscle, lameness can be appeared after behavior and social changes like augmented dreadfulness, extended recovery from the worrying situation, a decreased attention in social activities, games or toys (Moreau M *et al.*, 2003) ^[16]. The signs for chronic pain in dogs cannot be seen directly. Further, the behavior and reactions to chronic pain may vary from pet to pet. In this study, chronic pain was measured using CBPI as a primary endpoint and the quality of life as a secondary endpoint.

Among many fatty acid amide in the nature, PEA is one of them and acts as an essential agent in relieving the body's pain and inflammation regulation (Impellizzeri D *et al.*, 2009) ^[17]. The mechanism of action of PEA combination includes inhibition of inflammatory mediators, modulation of pain signaling, inhibition of mast cell activation, inhibition of fatty acid amide hydrolase and neuroprotection (De Filippis D *et al.*, 2011) ^[18]. Considering the effectiveness of PEA combination, the current trial was performed to examine its efficacy and safety in the dogs suffering from chronic pain.

The physical examination was conducted at every visit to evaluate any change in physical parameters due to PEA combination. At the baseline, all the physical parameters were normal indicating all the dogs were in healthy condition. No any significant difference was observed in any of the physical parameter at Day 14 and EOS as compare to baseline inferencing that the PEA combination is having no any harmful effects on functioning of body system. The blood reports of all dogs were in normal range indicating the healthy status of each pet at baseline.

Similarly, the assessment of body condition score was performed on every visit to evaluate the changes in body condition score. For all the dogs, the BCS remained same at the EOS as compare to baseline. Based on the result of body condition score, it was concluded that there is no any deteriorating effect nor improving effect of PEA combination on body condition.

PEA combination showed significant reduction in total CBPI (reduction by -31.42 points, $p < 0.001$) at EOS as compared to the baseline indicating an improvement in dogs' chronic pain condition. The total CBPI score is based on the summation of PSS and PIS. Hence, a substantial difference in the score of pain severity as well as pain interference was observed between the Day 0 and 28. PEA combination showed significant reduction in pain severity score from 27.58 on Day 0 to 16.41 on Day 28 (reduction by -11.17 points, $p < 0.001$). This reduction showed a marked improvement in the severity of pain due to the treatment of PEA combination. Similarly, PEA combination showed significant reduction in the score of pain interference from 47.66 on Day 0 to 27.41 on Day 28 (reduction by -20.25 points, $p < 0.001$). This reduction also presented a noticeable development in the interference of pain during routine function. The findings prove the usefulness of PEA combination, in treating chronic pain in dogs by reducing pain severity as well as pain interference in routine function of life. One study found that the PEA in combination with quercetin decreased the severity of pain, enhanced the locomotor activity, decreased the signs of swelling and mediators and the score of damage (histologically) was lowered and showed promising result for managing the multimodal pain seen in dogs and Osteoarthritis (OA) seen in rats displaying good-to-excellent safety and tolerability of PEA (Britti D *et al.*, 2017) ^[19]. In another study, PEA was

seen as an effective agent as anti-inflammatory and as a neuropathic pain reducer in hyperalgesia (Seol TK *et al.*, 2017) ^[20]. In one noticeable study, the effectiveness of PEA was observed in chronic OA dogs. The dogs were also having the persistent lameness since last one month. The dogs were given 4 weeks of treatment of complementary feed with PEA and quercetin. The result showed significant decrease in CBPI scores throughout the study and a significant recovery in lameness was observed due to study treatment (Vezzoni A *et al.*, 2018) ^[21].

The treatment with PEA combination showed a development in QoL in the dogs, with significant improvement seen at Day 28 with comparison to Day 0. The significant reduction in QoL score from 21.41 on Day 0 to 7.58 on Day 28 (reduction by -13.83 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 10.08 on Day 0 to 3.50 on Day 28 (reduction by -6.58 points, $p < 0.001$) indicating a noticeable improvement in the family's concern. Many times, the long lasting disease process results into asymptomatic chronic pain. The feelings of the pain induce the changes in the animal behavior, which may often be ignored by the owner (Karpiński M *et al.*, 2021) ^[22].

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

Conclusion

PEA combination significantly decreases the severity of pain and enhanced the score of quality of life of dogs. PEA combination also demonstrated to be safe and tolerable as no major adverse event was occurred during the study course.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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