The Beneficial Effect of Two Nutraceuticals in Flea Allergy Dermatitis Itch Control: A Comparative Study

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Abstract

This prospective randomized double-blinded multicentric study aimed to assess the efficacy of a new nutraceutical in controlling itch and skin lesions caused by flea allergy dermatitis (FAD) and compare it with another oral product of proven efficacy.

Forty-three dogs, of different age, breed and sex, with FAD were included and divided into two groups: 24 received product A and 19 product B. Both groups received the same antiparasitic treatment. A modified canine atopic lesion index (mCADLI) and pruritus visual analogic scale (pVAS) were recorded at days 0, 30 and 60. pVAS was evaluated both by the examining veterinarian (vpVAS) and the owner (opVAS). Results obtained were compared between the two groups at each time point.

In both groups of dogs, a significant decrease of mCADLI, vpVAS and opVAS at day 30 and 60, compared to day 0, was observed. At baseline, the mCADLI scores of Group B were significantly higher than Group A (95% CI: -4.0 to 0.0, $p < 0.05$), with no differences at D30 and D60 (not significant, $p > 0.05$). In Group B, significantly lower values of vpVAS were observed at D30 compared to Group A (95% CI: -2.5 to 0.0, $p < 0.05$), but not at D60 (not significant, $p > 0.05$). The median values of pVAS in Group B were lower compared to Group A at both D30 (95% CI: -2.5 to 0.4, $p < 0.01$) and D60 (95% CI: -3.0 to 0.3, $p < 0.05$).

Both nutraceuticals can be useful to control discomfort, skin lesions and pruritus due to flea allergy dermatitis and can be a valuable replacement for antipruritic drugs antihistamines, steroids or Il-31 inhibitors.

Introduction

Flea allergy dermatitis (FAD) is a common pruritic skin disease in dogs and cats. Flea infestation and FAD are different entities: a flea infestation is associated

with the presence of an unusually high number of fleas, whereas in dogs with FAD their number is usually very low [1] Four different types of allergic reactions to flea saliva have been reported: type I (immediate), type IV (delayed), basophilic hypersensitivity, and late IgE-mediated response [1]. Dogs affected by FAD can have different skin lesions, mainly in the lumbosacral region, inguinal areas, and thighs [2,3]. Primary skin lesions are represented by erythema and papules, while secondary skin lesions span from self-induced alopecia to crusts and pyotraumatic dermatitis with secondary bacterial skin infections. In more severe and chronic cases, skin lesions can be characterized by hyperpigmentation, seborrhoea, and deep skin infections; in rare cases fibro-pruritic nodules can be detected on lumbosacral area, along with alopecia and skin hyperplasia [1,2,3]. Flea allergy dermatitis diagnosis can be achieved by direct ectoparasite identification, coat brushing, and intradermal or serologic allergy testing [1,4,5].

Many antiparasitic treatments are registered to kill fleas and they exist in different forms as collars, spot-on, tablets, sprays, etc. Insect growth regulators and/or insect development inhibitors are generally added to control flea infestation in the environment [6,7,8,9]. Itch induced by flea allergy induces discomfort and stress to allergic or infested dogs. So, many antipruritic drugs are commonly used to decrease skin lesions and itch in association with antiparasitic therapy [10,11]. These are commonly represented by antihistamines, steroids or Il-31 inhibitors [1,7,12]. In less severe cases nutraceuticals with anti-inflammatory effects can be used to decrease skin inflammation and pruritus.

Essential fatty acids (EFAs) and aliamides have a well-known anti-inflammatory effect and they are used for many allergic skin diseases to control erythema and itch [1,13]. Essential fatty acids can downregulate inflammatory prostaglandins and leukotrienes, decrease TEWL (trans epidermal water loss), and have a steroid-sparing effect [1,7,14]. Blackcurrant oil is a natural source of polyunsaturated fatty acids (PUFAs), especially gamma-linolenic acid and stearidonic acid, with some natural anti-pruritic effects [7]. Aliamides, as palmitoylethanolamide (PEA), are endocannabinoid “like” mediators. They decrease proinflammatory chemokine release and mast cell degranulation [13,15]. Endocannabinoids receptors are expressed in many tissues and can regulate homeostatic functions and physiologic processes [16]. Cannabinoids (CBCs) can mitigate inflammatory skin reactions and can be used to control pruritic skin diseases such as atopic dermatitis [16,17].

Aims of this prospective randomized double-blinded multicentric study, were:

To evaluate the anti-pruritic efficacy of a new nutraceutical based on blackcurrant oil, hemp oil and vitamin E on dogs affected by FAD (product A).

To compare the efficacy of this nutraceutical to a competitor composed of palmitoylethanolamide and biotin commonly used in itch control (product B).

Materials and Methods

Study design

This study was designed following good clinical practices, although no suffering or health risks to the dogs were anticipated. The study was approved by the ethical committee of the Department of Veterinary Medicine of authors university. Ethical review was not necessary since requirements for administration of a nutraceutical are covered in the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, which exempt it from ethics approval. The study was designed as a prospective randomized double-blinded multicentric study.

Inclusion and exclusion criteria

To be included in the study dogs should have a diagnosis of FAD, be aged between 1 and 12 years, and weighing between 1 kg and 20 kg. Furthermore, other parasitic infestations, microbial infections, autoimmune or immune-mediated diseases, metabolic or hormonal disorders had to be previously excluded. No ectoparasitic treatment had to be administered at least for 30 days (in the case of long-acting products at least 90 days). No any kind of nutraceutical with antiinflammatory or antipruritic effect have to be administered during the last 30 days. A written consent had to be signed by the owner to include his/her dog in the study for 2 months. To be eligible for the study the modified CADLI score had to be lower than 10 (in order to exclude severe cases that may need stronger antipruritic treatments with drugs).

Dogs with a diagnosis of FAD treated with systemic or topical antibiotics, steroids, IL-31 inhibitors, or antihistaminics were excluded as well as those receiving nutraceuticals in the last 30 days before inclusion.

In case of worsening of the clinical signs, appearance of new skin or systemic diseases, changes of diet, or unwillingness of the owner to continue the administration of product A or B, the selected dogs were dropped out of the study.

Experimental procedure

The nutraceuticals involved in the study were commercially available oral products containing a combination of several active ingredients. Product A was a capsule containing 250 mg of blackcurrant oil in 20% of gamma-linolenic acid (GLA), 50 mg of hemp oil in 10% of cannabidiol (CDB) and 5000 IU of Vitamin D3. Product B was a capsule containing 7,53% of palmitoylethanolamide (PEA), and 754 mg/kg of Biotin.

A simple randomization has been used: a random allocation sequence to treatment A or treatment B was created.

On day 0 the dogs that fulfilled inclusion/exclusion criteria were evaluated by the examining veterinarian with a modified Canine Atopic Dermatitis Lesion Index (mCADLI) [18]. This modified score focused on neck, dorsum, ventral region and tights [9,19]. Visual Analogic Scale for pruritus (pVAS) [20] was performed by both the owner (opVAS) and the veterinarian (vpVAS).

Each subject was then randomize allocated to the group receiving product A or B.

Product A was dispensed in reason of 1 pearl day every 10 kg of body weight (bwt), according to manufacturer instructions; while the dose of product B was 1 pearl day every 6 kg, 2 pearls every 7-12 kg, 3 pearls every 15 kg and 4 pearls every 20 kg, according to manufacturer instructions.

On day 0 all selected dogs received from the enrolling veterinarian 1 pill of lotilaner following the dose reported in Table 1 and a flumethrin plus imidacloprid collar (table 1a) as antiparasitic treatment. Two

Table 1. Dosage of Lotilaner according to the label instructions.

Dogs' body weight	Lotilaner dose in mg/dog
1,3-2,5 kg	56,25 mg
>2,5-5,5 kg	112,5 mg
>5,5-11 kg	225 mg
>11-22 kg	450 mg

Table 1a. Dosage of Imidacloprid/Flumethrin according to the label instructions.

Dogs' body weight	Imidacloprid and flumethrin dose
<8 kg (38 cm collar)	Imidacloprid 1,24 g plus flumethrin 0,56 g
>8 kg (70 cm collar)	Imidacloprid 4,5 g plus flumethrin 2,03 g

different forms of antiparasitic treatments have been used in order to achieve three goals: treating fleas, preventing infestation with any other kind of parasites, such as mites, and protecting the dog from sandflies and consequent risk of leishmania (since the study has been conducted in an endemic country). The owners were instructed on how to perform the correct administration of product A or B and a new visit on day 30 was scheduled.

On days 30 and 60, a physical examination of the dogs was performed to assess general health, mCADLI, opVAS and vpVAS. Furthermore, the examiner veterinarian controlled the presence of any deviation from the protocol and that the owner correctly administered the assigned product. Antiparasitic treatment with lotilaner was directly administered by the examining veterinarian. If changes in the dog's general health conditions or protocol deviation were reported, the dog was excluded from the study.

Data analysis

Statistical analysis was performed using the software GraphPad Prism V.6.01. All data were evaluated using standard descriptive statistics and reported as mean ± standard deviation (sd) or as median and range (minimum-maximum), based on their distribution. Normality was checked using the D'Agostino Pearson test. Related variables from the same group were compared using repeated measure one-way analysis of variance or a Friedman test and a post hoc test (Holm-Sidak test or Dunn test) was performed.

Data obtained from the two different study groups were compared using unpaired t test or Mann-Whitney test. A P value<0.05 was considered significant.

Results

Forty-three dogs with FAD were included and completed the study, of those 24 received product A and 19 product B. Dogs belonging to the study groups were matched for sex (p=0.45), age (mean group A 5.5 years ±3.9 vs mean group B 4.9 years ±3.1, p=0.57) and bodyweight (mean group A 8.9 kg ±5.0 vs mean group B 8.7 kg ±6.2, p=0.87).

The dogs were of different breeds and sex (Table 2, Table 3).

The average age of the dogs included was 4,9 years (1 to 11 years) and 5,2 years (1 to 12 years) respectively for group A and B.

In both groups, a significant decrease of mCADLI, opVAS and vpVAS at days 30 and 60, compared to day 0, was observed. No differences were recorded in these values between day 30 and day 60 (Table 4, Table 5, Table 6).

At baseline, the mCADLI scores of Group B were significantly higher than Group A (95% CI: -4.0 to 0.0, $p < 0.05$), no differences were present at D30 and D60.

No differences were observed in opVAS and vpVAS between the study groups at baseline. In Group B,

Table 2. Signalment of animal included in group A

breed	n°	sex
Poodle	2	m
Boxer	1	nm:
Chihuahua	3	1f, 2m
Cocker spaniel	1	f
Golden retriever	1	m
Jack russel terrier	1	m
Lagotto	1	f
Italian greyhound	1	nf
Maltese	1	f
Mixed breed	10	6f, 2nf,2 m
Shiba inu	1	m
Pomeranian	1	f

m: male; nm: neutered male; f: female; nf: neutered female.

Table 3. Signalment of animal included in group B

breed	n°	sex
Cavalier king charles spaniel	1	m
Chihuahua	2	1m, 1f
Jack russel terrier	2	2 f
Maltese	1	f
Lagotto	1	f
Mixed breed	12	4 f, 1 nf,6m, 1 nm

m: male; nm: neutered male; f: female; nf: neutered female.

Table 4. Canine Atopic Dermatitis Lesion Index (mCADLI) scores recorded in the two study groups during the study. Values are expressed as median with minimum and maximum in brackets. Statistical significance is shown.

CADLI	D0	D30	D60	P value
Group A	5 (2-10)	2 (0-5)	1 (0-4)	$<0.05^{a}$; $<0.0001^{b}$
Group B	6 (2-12)	4 (0-6)	1 (0-5)	$<0.01^{a}$; $<0.0001^{b}$
P value	<0.05	ns	ns	

ns: not significant. a significant difference between D0 and D30. b significant difference between D0 and D60

lower values of vpVAS were observed at D30 (95% CI: -2.5 to 0.0, $p < 0.05$) but not at D60, while the median values of opVAS in Group B were lower compared to Group A at both D30 (95% CI: -2.5 to 0.4, $p < 0.01$) and D60 (95% CI: -3.0 to 0.3, $p < 0.05$).

Table 5 Examiner veterinarian Visual Analogic Scale (vpVAS) scores recorded in the two study groups during the study. Values are expressed as median with minimum and maximum in brackets. Statistical significance is shown.

vpVAS	D0	D30	D60	P value Friedman test
Group A	4.6 (2.5-7)	1 (0-4.3)	0 (0-6.4)	<0.001[a]; <0.0001[b]
Group B	4.7 (2.4-10)	2.5 (0-6)	0.8 (0-8)	<0.05[a]; <0.001[b]
P value Mann-Whitney test	ns	<0.05	ns	

ns: not significant. a significant difference between D0 and D30. b significant difference between D0 and D60.

Table 6. Owner Visual Analogic Scale (opVAS) scores recorded in the two study groups during the study. Values are expressed as median with minimum and maximum in brackets. Statistical significance is shown.

opVAS	D0	D30	D60	P value Friedman test
Group A	4.5 (4-8.4)	2 (0-4.5)	0 (0-6.5)	<0.001[a]; <0.0001[b]
Group B	6.5 (2.5-10)	3.8 (0-6)	2 (0-8)	<0.01[a]; <0.0001[b]
P value Mann-Whitney test	ns	<0.01	<0.05	

ns: not significant. a significant difference between D0 and D30. b significant difference between D0 and D60.

Discussion

Flea allergy dermatitis is a common pruritic disease in dogs. The affected animals can have skin lesions of different severity as papules, crusts, excoriations, self-induced alopecia and secondary skin infections. As for the other pruritic skin diseases the diagnosis is based on identification and/or exclusion of fleas based on effective flea control [1,2,3,4,5,6,7,8,9]. Subjects included in this prospective study had a previous diagnosis of flea allergy dermatitis based on these criteria. Other parasitic or allergic diseases have been excluded before the inclusion. All the animals selected received the same antiparasitic therapy to decrease the BIAS for statistical analysis.

Itch create a great discomfort and the decrease and control of it can be obtained through different treatments, depending on the severity of skin lesions. In mild cases essential fatty acids and/or aliamides can be useful to control erythema and decrease symptoms. In more severe cases, steroids and IL-31 inhibitors are of choice, alone or associated with nutraceuticals. This study included only dogs with mild pruritus related to FAD [1,3,7] associated with mild skin lesions.

Supplementation with dietary essential fatty acids is commonly recommended in allergic skin diseases such as flea allergy dermatitis and atopic dermatitis. Nutraceuticals help to improve the skin barrier and decrease water loss as well as decrease the production of inflammatory cytokines and inflammation [7,21]. Skin inflammation can be affected by omega 3 and 6 fatty acids (FAs): ω-6 FAs are transformed into prostaglandins (PG) E-2 and leukotriene-4, while ω-3 FAs are changed into PGE-3 and leukotriene -5 that are less pro-inflammatory than their corresponding ω-6 fatty acid isomers. Neutrophil activation is hindered by these newly synthesized ω-3 based mediators resulting in a reduction of allergic response [7,21,22]. In this study we used a nutraceutical enriched in blackcurrant oil. This vegetable oil

is a natural source of polyunsaturated fatty acids (PUFAs), especially gamma-linolenic acid and stearidonic acid. Previous studies have demonstrated the efficacy of black currant oil in decreasing pruritus and erythema in atopic dogs [7,21].

Hemp (*Cannabis sativa*) is an angiosperm plant belonging to the *Cannabaceae* family. Hemp contains a large number of compounds, such as phytocannabinoids, flavonoids, amino acids, fatty acids, vitamins, etc. [23]. The endocannabinoid system (ECS) is present in many species: from mammals to more primitive phyla (Cnidaria). The pervasive and early emergence of ECS in the evolution of life indicates its biological importance. ECS is composed of endogenous ligands, G-protein-coupled receptors (CBR) and a group of enzymes to degrade and recycle the ligands. Some of the receptors can modulate a healthy immune response by increasing anti-inflammatory and decreasing pro-inflammatory pathways. CBRs are able to induce apoptosis of T cells and induce inhibition of T cell proliferation while promoting the production of regulatory T cells. CBRs can be activated also by plant cannabinoids: phytocannabinoids can induce apoptosis of immune cells by activation of CD95, increase the production of the anti-inflammatory cytokine IL10 and reduce TNF-α and other pro-inflammatory cytokines [24]. Cannabidiol (CBD) is the main non-psychotropic cannabinoid found in *Cannabis sativa*. In recent years CBD has been used as a nutraceutical for its high content of polyunsaturated fatty acids (especially ω-3 series) and phenolic compound as a support in inflammatory diseases in dogs and humans [23]. Cannabidiol has been used in atopic dogs as an adjunct therapy to decrease pruritus with good results [25].

The association between blackcurrant oil and CBD oil tested in this prospective study was useful in decreasing the clinical signs of FAD. Even if control of the allergic response to flea bites is obtained by preventing parasite feeding with antiparasitic treatment, this treatment alone is not enough to decrease the erythema, pruritus and secondary self-induced skin lesion already present. Product A was able to decrease the opVAS ($p < 0.001$), vpVAS ($p < 0.001$) and mCADLI ($p < 0.05$) already during the first month of use.

Vitamin E is a fat-soluble nutrient that is essential for animal's body to develop strong and healthy muscles and healthy circulatory and immune systems. It's also an antioxidant, helping to protect cells from damage caused by free radicals. In dogs with excessive moulting, thin or balding patches on their coat, and dry or flaky skin, Vitamin E supplementation may improve the conditions [26]. In more recent years it has been reported to contribute to decrease many other inflammatory diseases of dogs and cats [27,28]. The presence of vitamin E can contribute to the anti-inflammatory effects of the formulation.

Palmitoylethanolamide (PEA), belongs to aliamides, a family of fatty acid amides whose name comes from their mechanism of action, the Autacoid Local Injury Antagonism (ALIA) [23]. PEA is a bioactive lipid compound and an endocannabinoid-like molecule. Endocannabinoids and their mediators, such as PEA, are produced in response to inflammation and tissue damage and play a key role in controlling cutaneous inflammation and immunity [13]. PEA is generally used in allergic skin diseases with moderate clinical signs to decrease pruritus and skin lesions. In cats, this nutraceutical has been proven to decrease clinical signs of allergic dermatitis and reduce the use of systemic steroids [29]. Even if there are no specific indications for its use in canine FAD, the anti-inflammatory effects are well known [30]. In this study, all the dogs that received the product based on PEA had a significant decrease of opVAS ($p < 0.05$), v pVAS ($p < 0.01$) and mCADLI ($p < 0.01$) within the first month of treatment.

Active nutraceutical components of products A and B are commercialized respectively in pearls and capsules with inactive gel components. These forms of presentation are necessary to avoid oxidation of active components.

This study has some limitations. Forty-three dogs are a small group of dogs for a prospective study but FAD is an uncommon diagnosis nowadays in developed countries, thanks to extensive use of antiparasitic treatments. Animals selection was performed by a veterinary dermatologist as a guarantee of the correct diagnosis. It could have been useful to compare the efficacy of tested products in decreasing pruritus with a group of dogs treated only with antiparasitic drugs ("control group"), but this was avoided to diminish animal discomfort. Skin allergic reaction can decrease only by avoiding exposure to fleabite, but secondary lesions due to itch are responsible for major dog discomfort and can lead to skin barrier damage, alopecia, crusts and secondary skin infections. Despite extensive research and always new antiparasitic drugs flea infestation is still a major problem in lots of countries. 95% of the flea population is represented by immature stages present in the environment versus only 5% of adults on the host. Pupal stages can survive a long time without animal presence and are highly resistant to challenging environmental conditions, together with the high and fast rate of population growth provide excellent explanations for failure of parasite control [31]. For all these reasons, even with complete systemic antiparasitic treatment is impossible to achieve a quick control of the environmental infestation and a recrudescence of itch, in allergic dogs can be expected during the third week of treatment. In study trials two to four months are necessary to achieve complete flea control and subsequent remission of clinical signs of FAD in animals housed in infested environments [10]. Even with a complete antiparasitic treatment allergic reaction takes time to decrease. As a confirmation of this hypothesis, at day 30 some of the included dogs had still positive pVAS and mCADLI values. FAD affected dogs generally receive antiinflammatory drugs such as steroids or IL-31 inhibitors to decrease inflammatory reactions and avoid self-inflicted skin lesions [1,7,12]. Nutraceuticals with antiinflammatory action can avoid the use of systemic drugs in mild cases.

Another limitation of the study is related to the different age, sex and breed of the selected dogs. It was not possible to assess by statistical analysis if differences in these parameters had influenced the results, but the decrease of mCADLI, opVAS and vpVAS in both groups seems to confirm that age, sex and breed are not significant on the success of the nutraceutical anti-pruritic effects.

Conclusions

Flea allergy dermatitis is a pruritic allergic skin disease affecting dogs and cats. Antiparasitic therapy is mandatory to avoid immunologic stimulation, but it is not enough to decrease discomfort, skin inflammation and secondary skin lesions associated with pruritus. The study results highlight the efficacy of both products A and B in decreasing clinical signs (mCADLI) and pVAS in dogs affected by FAD, avoiding the use of steroids or IL-31 inhibitors. These results suggest that nutraceuticals with antiinflammatory and antipruritic effects can be an alternative therapy to decrease pruritus in dog's allergic skin diseases.

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Conflicts of Interest

L.C., A.G., G.P. and P.P. have been involved as a consultant witness in Company NBF Lanes.

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