

# Effect of Two Therapeutic Foods in Dogs with Chronic Nonseasonal Pruritic Dermatitis

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**KEY WORDS:** Dermatitis, dog, diet, novel protein, fish oil

## ABSTRACT

This study examined the effects of therapeutic intervention with diets containing a combination of a novel protein, fish oil, and elevated antioxidants in dogs with chronic nonseasonal pruritic dermatitis. A total of 101 pet dogs suffering from chronic nonseasonal pruritic dermatitis were recruited from 18 privately owned veterinary hospitals for a prospective, multi-site, clinical study. In their home setting, the dogs were fed diets containing either a salmon- or venison-based diet that was supplemented with fish oil and antioxidants. At 0, 4, and 8 weeks, veterinarians scored erythema, lichenification, and excoriation at 15 defined sites, and pet owners used a visual analogue scale to evaluate the severity of face rubbing, scratching/itching, licking, head shaking, ear scratching, skin redness, skin & coat condition, hair sheen, hair loss, and scaling. In dogs completing the study according to protocol (n=74), veterinarians found that erythema,

lichenification, and excoriation improved over time for dogs on both diets ( $P < 0.0001$ ). In addition, veterinarians reported improvement at study end for both the salmon- and venison-based diets in erythema (>69% of skin sites and >78% of dogs), lichenification (>61% of skin sites and >79% of dogs), and excoriation (>81% of skin sites and >80% of dogs). Owners also reported significant improvements over time in all scores ( $P \leq 0.02$ ) for both diets. These results show that nutritional intervention using a therapeutic diet containing a novel protein, fish oil, and elevated antioxidants improves clinical signs in dogs with chronic nonseasonal pruritic dermatitis.

## INTRODUCTION

Chronic nonseasonal pruritic dermatitis in dogs is primarily due to atopic dermatitis (AD), an inflammatory and pruritic allergic skin disease common in pet dogs usually associated with environmental allergen-induced production of anti-antigen immunoglobulin E.<sup>1</sup> More recently, a separate classification has been proposed of "atopic-like

dermatitis,” for which the signs are similar to AD, but immunoglobulin E-mediated hypersensitivity cannot be detected.<sup>2</sup> To further complicate the description of AD, the International Task Force on Canine AD considers that flares of AD may be triggered or aggravated by adverse food reactions (AFRs).<sup>3</sup> Furthermore, AFRs in dogs can occur as a chronic nonseasonal pruritic dermatitis that is difficult to distinguish from AD.<sup>3</sup>

In dogs, allergen-specific immunotherapy is considered effective in the treatment of at least AD. However, many of these dogs require long-term anti-inflammatory therapy with topical agents, antihistamines, cyclosporine, or glucocorticoids.<sup>4</sup> These therapies can be expensive, inconvenient to administer, and lead to adverse effects. Thus, there remains a need for safe, effective, and affordable alternatives to help manage dogs with chronic nonseasonal pruritic dermatitis. Nutritional intervention has been considered as an aid in the treatment of chronic nonseasonal pruritic dermatitis. For example, supplementation with fish oil, which is rich in omega-3 fatty acids, has been reported to have beneficial effects in dogs with pruritic skin disease.<sup>5-7</sup> In addition, antioxidants such as vitamin E, selenium, and  $\beta$ -carotene may also be useful in the treatment of pruritic skin disease.<sup>8-10</sup> Finally, switching dogs to diets containing novel protein sources such as fish or venison has been reported to help ameliorate signs of chronic nonseasonal pruritic dermatitis and improve overall skin and hair coat quality.<sup>6,11-13</sup>

Accordingly, we hypothesized that a therapeutic diet containing a combination of a novel protein, fish oil, and elevated antioxidants would aid in the treatment of chronic nonseasonal pruritic dermatitis in dogs. Here, we performed an 8-week study in the home setting to examine the effect of feeding two such combination diets to pet dogs with chronic nonseasonal pruritic dermatitis.

## **MATERIALS AND METHODS**

### **Study conduct**

This investigation was a prospective 8-week study performed in 18 privately owned

veterinary hospitals in the United States between November 2004 and April 2005. The study was conducted according to Hill's Pet Nutrition's Global Animal Welfare Policy, and the protocol was approved by the Hill's Pet Nutrition's Institutional Animal Care and Use Committee. Participating veterinary hospitals carried out the studies according to the general principles of Good Clinical Practice, and all clients gave written informed consent.

Adult pet dogs with a clinical diagnosis of chronic nonseasonal pruritic dermatitis were considered candidates for the study. The diagnosis of chronic nonseasonal pruritic dermatitis was based on the current guidelines at the time the study was performed, including history, typical clinical signs, and the ruling out other pruritic skin conditions.<sup>14,15</sup> To be included in the study, dogs had to have at least three of the following: 1. pruritus; 2. facial and/or digital involvement; 3. lichenification of the flexor surface of the tarsus or extensor surface of the carpus; 4. chronic or chronically relapsing dermatitis; 5. familial history of AD; 6. breed predilection; and 7. positive diagnosis of AFR based on an elimination trial.

Dogs were excluded if they had known AFRs or positive dietary elimination trials for venison, salmon, or potatoes; history of fish oil supplementation or consumption of foods supplemented with fish oil within 12 weeks of the start of the study; major concurrent systemic diseases (eg, diabetes mellitus, hypothyroidism, hyperadrenocorticism, or kidney failure); concurrent illness or disease that made completion of the 8-week feeding period unlikely; surgery anticipated or planned during the 8-week feeding period; pregnancy anticipated or planned; or fractious behavior. Allergen avoidance, allergen-specific immunotherapy, symptomatic anti-inflammatory therapy, and antimicrobial therapy were permitted as long as drugs, doses, and frequency of administration remained constant from the time of previous food administration through the completion of the study.

Other permitted medications included antimicrobial therapy, antihistamines, topical anti-inflammatory agents, cyclosporine, and glucocorticoids. Nutritional supplements such as vitamin supplements (without omega-3 fatty acids) were permitted. Dogs were removed during the course of the study if they had an adverse reaction that created a health risk; an adverse reaction, injury, or illness warranting a prohibited treatment and/or surgical intervention or required unmasking of the experimental treatment; a lack of dog owner compliance or owner withdrawal of dog from the study; unacceptable discomfort; death; or other loss to follow-up.

During the entire course of the study, dogs were living at home with their owners. Eligible dogs were randomly assigned to be fed one of two prototype foods containing potato and salmon (Prescription Diet® d/d® Canine Skin Support Potato & Salmon Formula; Hill's Pet Nutrition, Topeka, KS) or potato and venison (Prescription Diet® d/d® Canine Skin Support Potato & Venison Formula; Hill's Pet Nutrition, Topeka, KS), both of which were available in wet and dry forms. Neither pet owners nor investigators (primary care veterinarians) knew which diet the dog was to receive. Owners had the choice of feeding their dog dry food, wet food, or a mixture of the two. Upon enrollment in the study, pet owners were instructed to transition their dogs to the assigned study diet over a 7-day period by mixing increasing amounts of study food with decreasing amounts of the food used before entry in the study. Feeding guidelines were provided to pet owners with the intent that dogs be fed according to their usual feeding regimen (free choice or meal fed) to maintain a constant body weight and condition. At enrollment (week 0) and at weeks 4 and 8, the veterinarian evaluated the clinical severity of chronic nonseasonal pruritus using a modification (ie, fewer sites) of CADE-SI-02.<sup>4,16</sup> Briefly, a score (0, normal; 1, mild; 2, moderate; and 3, severe) was assigned to erythema, lichenification, and excoriation at 15 selected body sites, yielding a total lesion score of 0 to 45 and a total score of 0 to

135 for each dog. Erythema was used as an indicator of acute inflammation, lichenification as a marker of chronic inflammation, and excoriations as an indirect manifestation of pruritus. These definitions were stated in the study protocol, and investigators were informed of the definitions during training sessions.

The same veterinarian performed all assessments for a given dog. Also, veterinarians were required to record all adverse events as well as their severity and their apparent relationship with the study food. Dogs were removed from the study if their health was considered to be at risk.

At weeks 0, 4, and 8, owners assessed clinical signs for the 24 h preceding visits. Scoring was done using a visual analogue scale (200-mm line) with major graduations of 0 to 10 and legends to indicate anchors (eg, no face rubbing to face rubbing all the time). Clinical signs included the following: face rubbing; scratching/itching of the skin; licking of paws, armpits, groin, or anal region; head shaking; scratching of the ears; skin redness; condition of skin and hair coat; shininess of the hair; hair loss; or dandruff (scaling).

### **Statistical Analyses**

Data from veterinarian and pet owner evaluations were analyzed by analysis of variance (ANOVA) using PROC MIXED in SAS version 9.1.3 (SAS Institute, Cary, NC). A repeated measures design with an unstructured covariance pattern was fitted to the data. The Kenward-Roger procedure was used to correct for upward bias in the test statistics and downward bias in the standard errors resulting from random effects in the model and correlation between the repeated measurements. Analyses of improvements (yes/no) vs day 0 were analyzed on a per-skin site and a per-dog basis using PROC GLIMMIX in SAS for a binomial distribution, and standard errors were calculated. For the analysis on a per skin site basis, a random clinic effect was not significant and was not included in the final model. The according-to-protocol population included

all dogs completing the study according to protocol and not excluded ex post facto, and the intent-to-treat population included all dogs enrolled and fed one of the study diets. Except where noted, all data are reported as group means  $\pm$  standard error. For all analyses, a P-value below 0.05 was considered as indicating a significant difference.

## RESULTS

The nutritional content of the diets on a dry matter basis are shown in Table 1. The level of omega-3 fatty acids was higher and the omega-6-to-omega-3 fatty acid ratio was lower in salmon-based diet than in the venison-based diet. Also, the level of fat was slightly higher and the level of protein slightly lower in the salmon-based diet. Otherwise, the levels of measured nutrients were similar in the two diets.

A total of 101 dogs were enrolled and assigned food (intent-to-treat popula-

tion). Eight of the dogs were diagnosed with AFRs, and the specific cause of the chronic nonseasonal pruritic dermatitis was not known for the remaining 93. Thirteen dogs were dismissed during the course of the study (5 for owner compliance, 1 for concurrent medical condition, 2 for adverse episodes, 2 for use of inappropriate medications, and 3 for palatability problems). The remaining 88 dogs completed the 8-week study, although 14 had protocol violations (change in medication or dosage after the week 4 visit), so that 74 dogs completed the study according to protocol. In this population, there were no significant differences between dogs fed the salmon-based and venison-based diets in age at study start ( $6.0 \pm 0.5$  vs.  $6.5 \pm 0.6$  y), weight ( $20.8 \pm 1.9$  vs.  $18.3 \pm 2.2$  kg), body condition score ( $3.35 \pm 0.10$  vs.  $3.27 \pm 0.12$ ), male-to-female ratio (54% vs. 58% male), reproductive status

**Table 1.** Nutrient composition of the test diets

Component	Salmon-based diet	Venison-based diet
Protein	18.0%	16.9%
Total fat	15.2%	16.4%
Nitrogen-free extract (carbohydrate)	59.3%	59.5%
Crude Fiber	1.9%	1.7%
Calcium	0.9%	0.8%
Phosphorus	0.8%	0.6%
Magnesium	0.1%	0.1%
Potassium	1.1%	1.1%
Sodium	0.4%	0.4%
Total omega-6 fatty acids	2.9%	3.3%
Total omega-3 fatty acids	1.6%	0.8%
Omega-6:omega-3 ratio	1.9	4.2
Selenium, ppm*	0.56	0.61
Vitamin E, IU/kg*	1033	1007
$\beta$ -carotene, ppm*	3.1	3.1
Vitamin C, ppm*	241	240

Nutrients are expressed on a percent dry matter basis and were calculated on the basis of a 2:1 dry to wet feeding ratio, which was estimated from owner reports. Except for antioxidant levels, nutritional content was determined using chemical methods by Eurofins (Des Moines, IA).

\*Levels of antioxidants in the finished products were calculated according to the amounts added and after adjusting for estimated processing losses.

(100% vs. 89% intact), or use of concurrent medications (76% vs. 73%). There was also no difference in weight change ( $0.31 \pm 0.30$  vs.  $0.20 \pm 0.18$  kg) or change in body condition score ( $-0.05 \pm 0.07$  vs.  $-0.05 \pm 0.05$ ) over the 8-week study. Concurrent medications included corticosteroids (11% vs. 8%), antibiotics (14% for both diets), antifungals (5% vs. 8%), antihistamines (14% vs. 19%), immunosuppressants (5% vs. 0%), allergen-specific immunotherapy (8% vs. 3%), and combinations of different treatments (11% vs. 14%).

In the 74 dogs that completed the study according to protocol, all three veterinarian-assessed scores (erythema, lichenification, and excoriation) improved over time ( $P < 0.0001$ ), but there were no significant differences between the two diets (Table 2). Similarly, according to owners, dogs fed both diets exhibited significant improvements over time for all signs ( $P \leq 0.02$ ; Table 3), but there were no significant differences between the two diets. Use of concurrent medication did not significantly affect the improvements over time or the relative effects of the two diets on either veterinarian- or owner-assessed signs (data not shown). Results were similar when the analysis was repeated for the intent-to-treat population

( $n=101$ ), although scaling was no longer significantly different (data not shown).

According to investigators, at least 69% of skin sites showing erythema, 61% showing lichenification, and 81% showing excoriations improved or completely resolved for both diets (Table 4). Also, for both diets, at least 78% of all dogs showing erythema, 79% showing lichenification, and 80% showing excoriations improved (data not shown). Results were similar at week 4 on both a per-skin site and per-dog basis, as well as for the intent-to-treat population (data not shown).

In the subpopulation of dogs known to have AFRs ( $n=8$ ), at study end (week 8), 64% of skin sites in dogs on the salmon-based diet ( $n=5$ ) and 63% in dogs on the venison-based diet ( $n=3$ ) showed improved erythema. Respectively, 88% and 45% showed improved lichenification, whereas all sites showed improved excoriation. On a per-skin site basis, complete resolution was observed in 64% vs. 63% for erythema, 68% vs 26% for lichenification, and 100% vs. 61% for excoriation. Finally, worsening was observed in less than 10% of all sites for both diets. The results were similar at 4 weeks (data not shown).

**Table 2.** Veterinarian-assessed signs of pruritic dermatitis in dogs completing the study according to protocol and fed the salmon-based diet ( $n=37$ ) or the venison-based diet ( $n=37$ )

Score	Diet	Week 0	Week 4	Week 8	P-value Food	P-value Time
Lesion score (0-135)	Salmon	23.7±2.5	14.0±2.6	12.1±2.4	0.91	<0.0001
	Venison	24.1±2.5	14.5±2.6	12.2±2.4		
Erythema (0-45)	Salmon	8.8±1.0	5.4±1.0	5.0±1.1	0.44	<0.0001
	Venison	8.6±1.0	4.8±1.0	3.7±1.1		
Lichenification (0-45)	Salmon	10.8±1.6	6.4±1.4	5.7±1.4	0.56	<0.0001
	Venison	11.2±1.6	7.7±1.4	6.7±1.3		
Excoriation (0-45)	Salmon	4.6±1.0	2.7±0.8	1.9±0.7	0.85	<0.0001
	Venison	4.5±1.0	2.1±0.8	1.9±0.7		

*P-values were determined by ANOVA.*

**Table 3.** Owner-assessed signs of pruritic dermatitis in dogs completing the study according to protocol and fed the salmon-based diet (n=37) or the venison-based diet (n=37)

	Diet	Week 0	Week 4	Week 8	P-value Food	P-value Time
Face rubbing	Salmon	15.3±1.9	13.0±1.7	13.7±1.7	0.65	0.02
	Venison	16.4±1.9	11.4±1.7	11.2±1.7		
Scratching & itching	Salmon	23.3±1.8	14.9±1.5	15.9±1.7	0.26	<0.0001
	Venison	25.9±1.8	16.6±1.5	17.7±1.7		
Licking	Salmon	26.6±1.7	17.8±1.7	19.1±1.8	0.86	<0.0001
	Venison	26.1±1.7	18.6±1.7	19.9±1.8		
Head shaking	Salmon	15.2±2.0	10.4±1.6	10.8±1.7	0.59	0.0004
	Venison	16.8±2.0	11.6±1.6	11.4±1.7		
Ear scratching	Salmon	18.2±1.9	11.2±1.5	12.2±1.8	0.57	<0.0001
	Venison	20.1±1.9	12.1±1.5	12.9±1.8		
Skin redness	Salmon	17.7±1.9	10.5±1.5	10.9±1.7	0.95	<0.0001
	Venison	16.4±1.9	10.8±1.5	11.5±1.7		
Skin & coat condition	Salmon	15.8±1.7	13.7±1.6	12.6±1.7	0.18	<0.0001
	Venison	21.8±1.7	13.9±1.6	14.5±1.7		
Hair sheen	Salmon	18.7±1.7	14.6±1.6	14.8±1.7	0.47	0.001
	Venison	20.2±1.7	15.7±1.6	16.5±1.7		
Hair loss	Salmon	18.5±1.8	13.9±1.6	12.7±1.7	0.55	<0.0001
	Venison	21.6±1.8	15.1±1.6	12.0±1.7		
Scaling	Salmon	11.9±2.1	10.2±1.7	11.4±1.8	0.42	0.02
	Venison	15.9±2.1	11.6±1.7	11.5±1.8		

P-values were determined by ANOVA.

**Table 4.** Percent of skin sites with no change, worsening, improvement, or complete resolution at study end (week 8) in dogs completing the study according to protocol and fed the salmon-based food (n=37) or the venison-based food (n=37)

Sign	Food	Sites showing signs at study start				All sites
		Complete Resolution (%)	Total Improved (%)	No change (%)	Worsened (%)	Worsened (%)
Erythema	Salmon	60	69	22	9	9
	Venison	69	75	23	2	6
Lichenification	Salmon	52	74	24	2	4
	Venison	37	61	35	4	4
Excoriation	Salmon	74	82	14	3	4
	Venison	60	81	14	4	4

Erythema, lichenification, and excoriation were assessed at 15 specified sites on each dog. Complete resolution was defined as the absence of a given dermatological condition that had been present at week 0.

A total of 17 adverse events were reported in the intent-to-treat population (n=101). Three adverse events were thought to be related to the study food. These included two cases of vomiting (one each for the salmon- and venison-based diets) and one case of persistent scratching (salmon-based diet). All three of these dogs were removed from the study because these adverse events were considered severe enough to be considered a health risk. Three additional adverse events were considered possibly related to the study diets. All of these were for dogs on the venison-based diet. They included two dogs with pruritus of the ears that were treated with antibiotics and were dismissed from the study due to the use of additional medications. The third dog had pruritus of the paws that cleared up without additional treatment.

## DISCUSSION

The current study showed that therapeutic diets containing novel proteins, fish oil, and elevated antioxidants improve signs in dogs with chronic nonseasonal pruritic dermatitis. Clinical signs were assessed by veterinarians at 15 sites using a modified version of CADESI-02, which was the most up-to-date scoring system at the time the study was performed.<sup>4,16</sup> Also, owners assessed signs using a visual analogue scale, a system often employed in clinical studies examining the effects of diet in canine AD.<sup>6,7,13</sup>

According to both veterinarians and owners, dogs fed both diets showed improvement in signs of nonseasonal pruritic dermatitis over time. In addition, as assessed by veterinarians, the majority of skin sites showing signs at study start showed improvement in self-trauma (excoriation), chronic changes (lichenification), and acute changes (erythema) by study end (week 8). Complete resolution of each sign at these sites was frequently observed, including at least 60% of the sites at week 8 according to the erythema and excoriation scores. On a per-dog basis, approximately four out of five showed improvement in all signs for both diets.

These percentages excluded sites and

dogs that did not show signs at study start because it was not possible for them to show any improvement. As this could have biased interpretation of the results, we also examined the percent of worsening at all sites (ie, both showing and not showing signs at study start). We found that for all signs, worsening occurred at less than 10% of all sites. In other words, excluding the sites or dogs not showing signs at study start did not influence the findings.

Because this study lacked a control diet, it was not possible to exclude the possibility of influence from factors other than the diets themselves, such as owners' and veterinarians' expectations for improvement, an improved level of care and attention, or the waxing and waning nature of AD. However, we consider it unlikely that viewer bias could have accounted for such a high level of response according to veterinarians, as they were scoring specific signs at distinct lesion sites. It is also not likely that the waning phase of AD was synchronized in such a large population of geographically dispersed dogs. Furthermore, our statistical analysis showed that the use of concurrent treatments did not influence the ability of the two diets to improve clinical signs of pruritus. Also, only four dogs were on allergen-specific immunotherapy, so this was not a major influence in this study. In other words, the observed improvements appear to be due to the diets themselves.

In most cases, the cause of the nonseasonal pruritic dermatitis was not known. In the eight dogs where the nonseasonal pruritic dermatitis was associated with an AFR, the majority of sites showed complete resolution of erythema for both diets, although the salmon-based diet appears to have been more effective than the venison-based diet for lichenification and excoriation. This could suggest a specific effect of fish oil omega-3 fatty acids or a selective effect of the protein source. However, there were not enough dogs with known AFRs to make a reliable statistical comparison.

The inclusion of a novel protein is likely

a major reason for the beneficial effects of the two diets, as switching dogs to novel proteins is now known to improve pruritic skin conditions in dogs.<sup>6,11-13</sup> Omega-3 fatty acids from the added fish oil in the diets may have contributed to the improvement in skin condition.<sup>5-7</sup> Overall, we found no differences in the effects of the two diets despite differences in their omega-3 fatty acid levels and in their omega-6:omega-3 fatty acid ratios, although there may have been differences in the subset of dogs with AFRs. Finally, the elevated antioxidant levels in the diets could also have contributed to the improvements, although there is currently a lack of clear evidence in support of an effect of oral antioxidants in pruritic skin diseases.

## CONCLUSIONS

This study shows that switching to one of the two diets described here can be an important part of a multimodal treatment approach in dogs with chronic nonseasonal pruritic dermatitis. Further studies are needed to determine the contribution of the different ingredients to the improvements.

## ACKNOWLEDGMENTS

This study was supported by Hill's Pet Nutrition, Inc. The authors thank Dr. Kristin Sixby and Heidi Schiefelbein for technical assistance, and also the following clinical investigators for participating in the study: W.H. Bentham, Fremont, CA; Paul Black, Rochester, NY; Kimberley Brasher, Nashville, TN; Eric Chafez, Vienna, VA; Charles Conley, Chattanooga, TN; Carmen Coats, Grand Rapids, MI; Bill Craig, San Antonio, TX; Ed Farnham, Kentwood, MI; Meg Gober, West Grove, PA; Marty Greer, Lomira, WI; Adele Mays, Farragut, TN; David Imbach, Porterville, CA; Susan Moon, Memphis, TN; Pamela Ogden, Eau Claire, WI; Susan Oltman, Ellicott, MD; Craig Prior, Nashville, TN; Jeffrey Schuett, Pewaukee, WI; and A. Jay Schweizer, Independence, MO.

## REFERENCES

- DeBoer DJ. Canine atopic dermatitis: new targets, new therapies. *J Nutr* 2004;134:2056S-2061S.
- Halliwell R. Revised nomenclature for veterinary allergy. *Vet Immunol Immunopathol* 2006;114:207-208.
- Olivry T, DeBoer DJ, Prelaud P, et al. Food for thought: pondering the relationship between canine atopic dermatitis and cutaneous adverse food reactions. *Vet Dermatol* 2007;18:390-391.
- Olivry T, Rivierre C, Jackson HA, et al. Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. *Vet Dermatol* 2002;13:77-87.
- Logas D, Kunkle GA. Double-blinded crossover study with marine oil supplementation containing high-dose eicosapentaenoic acid for the treatment of canine pruritic skin disease. *Vet Dermatol* 1994;5:99-104.
- Bensignor E, Morgan DM, Nuttall T. Efficacy of an essential fatty acid-enriched diet in managing canine atopic dermatitis: a randomized, single-blinded, cross-over study. *Vet Dermatol* 2008;19:156-162.
- Saevik BK, Bergvall K, Holm BR, et al. A randomized, controlled study to evaluate the steroid sparing effect of essential fatty acid supplementation in the treatment of canine atopic dermatitis. *Vet Dermatol* 2004;15:137-145.
- Duntas LH. Selenium and inflammation: underlying anti-inflammatory mechanisms. *Horm Metab Res* 2009. 41:443-447.
- Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. *Biochim Biophys Acta* 2005;1740:101-107.
- Thiele JJ, Ekanayake-Mudiyanselage S. Vitamin E in human skin: organ-specific physiology and considerations for its use in dermatology. *Mol Aspects Med* 2007;28:646-667.
- Leistra MH, Markwell PJ, Willemsse T. Evaluation of selected-protein-source diets for management of dogs with adverse reactions to foods. *J Am Vet Med Assoc* 2001;219:1411-1414.
- Roudebush P, Schick RO. Evaluation of a commercial canned lamb and rice diet for the management of adverse food reactions in dogs. *Vet Dermatol* 1995;5:63-67.
- Glos K, Linek M, Loewenstein C, et al. The efficacy of commercially available veterinary diets recommended for dogs with atopic dermatitis. *Vet*

*Dermatol* 2008;19:280-287.

14. Muller GH, Kirk RW, Scott DW. Immunologic Diseases In: Thomsett LR, ed. *Small Animal Dermatology*. Philadelphia, PA: W.B. Saunders, 1989;427-574.
15. Roudebush P, Guilford WG, Jackson HA. Adverse reactions to food. In: Hand, Thatcher, Remillard, et al., eds. *Small Animal Clinical Nutrition*. 5th ed. Topeka, KS: Mark Morris Institute, 2010;609-635.”
16. Ferguson EA, Littlewood JD, Carlotti DN, et al. Management of canine atopic dermatitis using the plant extract PYM00217: a randomized, double-blind, placebo-controlled clinical study. *Vet Dermatol* 2006;17:236-243.