ADVANCE VETERINARY DIETS

Research reports

A RESEARCH UPDATE
FOR THE VETERINARIAN
FROM AFFINITY PETCARE

CANINE ATOPIC DERMATITIS (CAD)

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Atopic dermatitis affects around 1 in every 10 dogs, and its incidence is increasing. In some breeds, such as the West Highland White Terrier or the French Bulldog, the prevalence exceeds 30%.

1. EPIDEMIOLOGY AND AETIOPATHOGENESIS OF CANINE ATOPIC DERMATITIS (CAD)

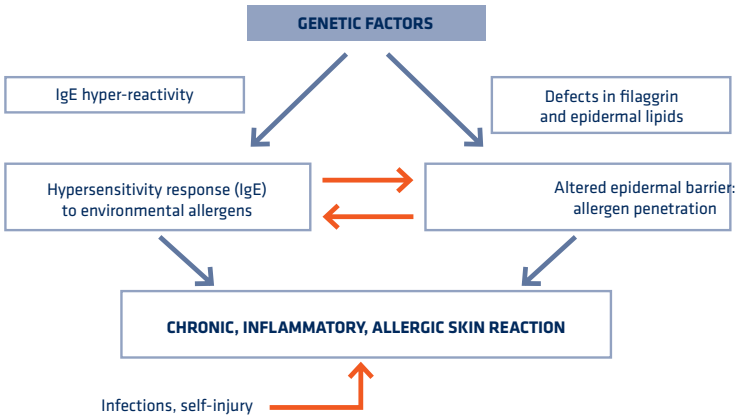
Atopic dermatitis is one of the most prevalent skin diseases in dogs. Although wide-ranging and conclusive epidemiological studies are unavailable, estimates show that 10–15% of dogs are atopic to some degree or another *(Hillier & Griffin, 2001)*. This figure is similar to that for atopic dermatitis in humans, with some authors reporting values of 15–20% in children *(Leung, 2003; Marsella & Girolomoni, 2009)*. Moreover, in some particularly predisposed breeds, such as the West Highland white terrier, French Bulldog or Shar Pei, the prevalence is higher still, exceeding 30% according to some authors.

This high prevalence, and the fact that this is a chronic disease, means that CAD is a problem commonly encountered in small animal clinics. Moreover, as this disease is **hard to diagnose and treat**, it can occasionally prove problematic for vets. Given the incidence and complexity of CAD, the *European College of Veterinary Dermatology* and the *American College of Veterinary Dermatology* decided to form a task force to better understand canine atopic dermatitis and improve its diagnosis and treatment *(Olivry, 2001)*. The *Task Force on Canine Atopic Dermatitis* defines CAD as an **"allergic, inflammatory, genetically programmed skin disease with defined clinical characteristics"** *(Olivry, 2001)*.

The pathogenesis of CAD is complex and probably differs between cases. Studies carried out in human atopic dermatitis, experimental models and in spontaneous cases of CAD have highlighted two main pathogenic mechanisms in atopic dermatitis (Figure 1): (a) hypersensitivity to environmental allergens, and (b) skin barrier alterations *(Marsella & Samuelson, 2009; Oyoshi et al., 2009)*.

Two main pathogenic mechanisms have been identified in atopic dermatitis: hypersensitivity to environmental allergens and skin barrier dysfunction

Figure 1. Schematic representation of the pathogenesis of CAD.



A. Hypersensitivity to environmental allergens

Atopic dermatitis has classically been considered as an allergy to environmental allergens, especially dust or storage mites, pollen, moulds and epidermal allergens *(Hill & de Boer, 2001)*. In addition, around a third of atopic dogs are also allergic to some component of their diet (proteins).

In short, atopic animals initially respond to percutaneous or mucosal contact with allergens by way of a humoral immune response that results in the production of specific IgEs. This response has been defined as a *T-helper-type-2* response in which the specific T lymphocytes produce IL-4, IL-5 and IL-13 and stimulate the synthesis of allergen-specific IgEs. These IgEs bind to the surface of skin mast cells via specific receptors and renewed contact with the allergens results in mast cell degranulation and the release of mediators such as histamine, prostaglandins or leukotrienes. In this model, which is shown in Figure 2, secondary infections (bacterial or by *Malassezia*) and scratching play a key role by perpetuating an active inflammatory response. In the chronic phase, the immune response changes to a *T helper-type-1* pattern with additional IFN-gamma production and the prolongation of the chronic pruriginous dermatitis *(Marsella & Samuelson, 2009)*.

While the primary cause of this abnormal immune response is unknown, it is clear that the main factor is a genetic predisposition to respond with IgEs. Indeed, researchers have identified that carriers of a certain gene tend to exhibit an IgE response when they come into contact with allergens (high-IgE responders). However, it is thought that numerous genes are implicated and these genes predispose the animal to develop humoral immune responses with an elevated IgE component.

B. Alterations to the skin barrier

In the last decade, a new paradigm has been developed to explain atopic dermatitis, namely **alteration to the skin barrier.** According to this paradigm, atopic dermatitis is at least partially due to epidermal barrier dysfunction. The epidermis is an effective barrier in which keratinocytes are sealed by the intercellular bridges (desmosomes) and an extracellular

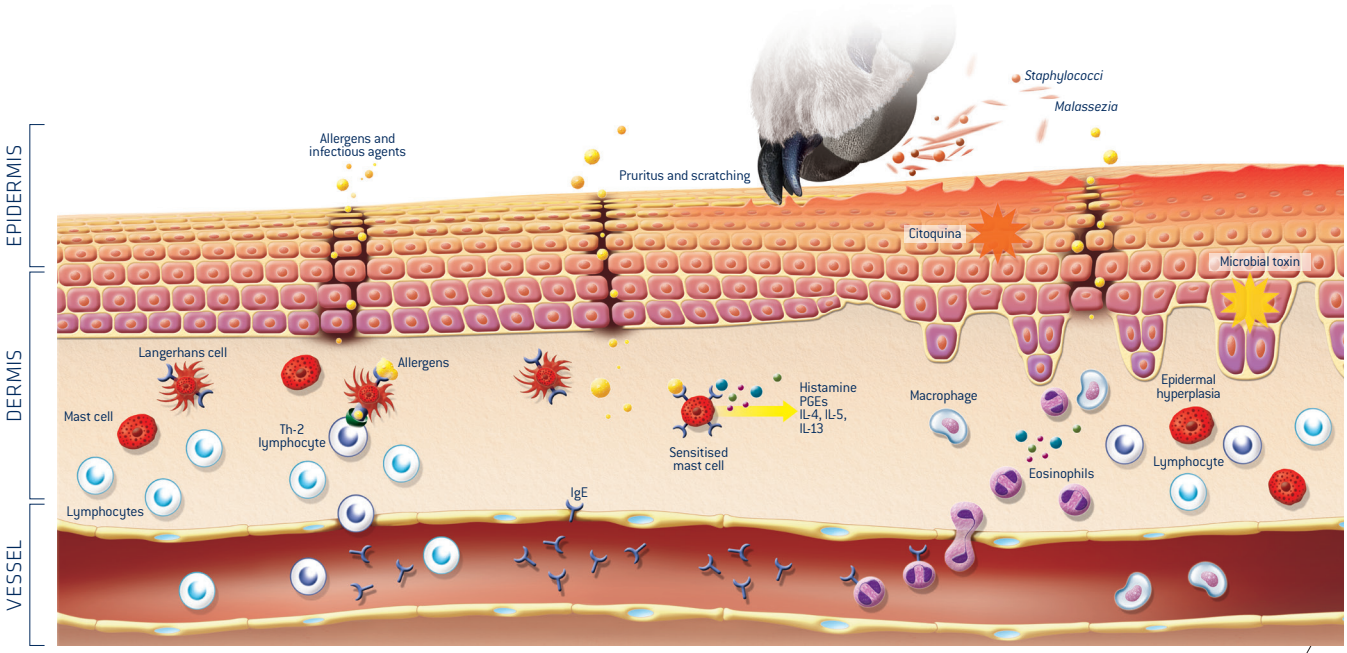


Figure 2. Progression of the inflammatory/allergic reaction in canine atopic dermatitis.

protein- and lipid-based cement (Figure 3). Any alteration to the insulating function of the epidermis, whether genetic or acquired, will allow greater penetration of the allergens and cause an abnormal immune response (hypersensitivity). It has been found that 30% of human atopic patients present a mutation in a protein known as filaggrin, which is one of the essential components required to construct the epidermal barrier. Alterations to enzymes that synthesise the complex lipids found in the stratum corneum (especially sphingosine) and proteases and enzymes have also been detected *(Popa et al., 2011)*.

Skin barrier dysfunction appears to be responsible for an increase in the percutaneous penetration of allergens and transepidermal water loss (TEWL), which may be responsible for the dryness typically observed in atopic dermatitis.

Thus, atopic dermatitis appears to be a clinical/pathological condition that can be reached via different pathways. However, in chronic phases, the barrier is altered in most individuals (partly due to inflammation and secondary infections) and there is also an allergic-type reaction (Figure 2).

Indeed, two variants of atopic dermatitis are recognised in humans and dogs. Thus, in humans, 80% of cases of AD are considered extrinsic, in other words, the immune response against an external allergen is considered the central phenomenon. These patients present high serum IgE levels. The remaining 20% of cases are considered to be "intrinsic", that is, patients do not present elevated serum IgE levels and skin barrier defects appear to be responsible for the clinical signs. Similarly, in dogs no specific IgEs are detected in 20% of cases of CAD, so the pathogenic mechanism is considered to be different. These cases are referred to as *atopic-like dermatitis (Marsella & Girolomoni, 2009)*.

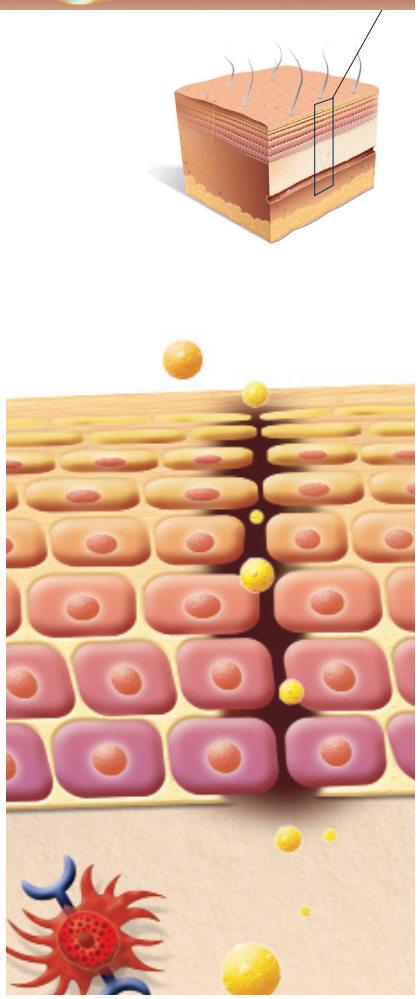
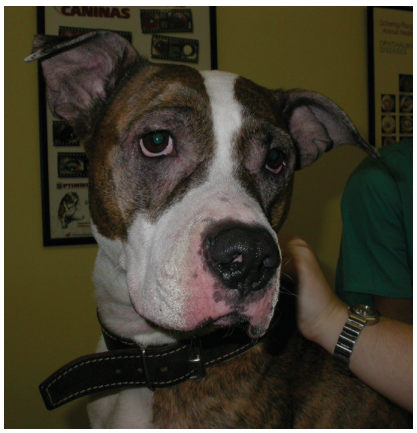


Figure 3. Structure of the skin barrier.

2. CLINICAL PRESENTATION AND DIAGNOSIS

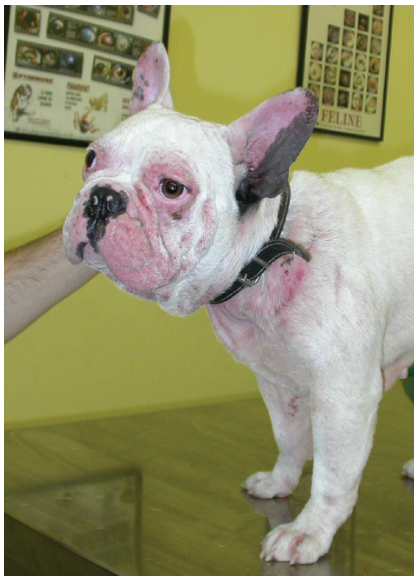
CAD is a disease of young dogs.
In 75% of cases the clinical signs appear aged 1 to 3 years old, with the disease normally persisting throughout the animal's life. In a small percentage of cases (less than 25%), it is seasonal and the clinical signs only appear for a few months each year, normally in spring and summer. None of the published studies have shown a predisposition in either sex, although breed does appear to be a factor, as is to be expected for a disease in the which genetics plays a key role. Although the breeds with such a predisposition may vary in different regions, most studies agree that **West Highland White Terriers, Boxers, Setters, Dalmatians, German Shepherds, Labradors, French Bulldogs and Shar Peis exhibit an above average incidence of CAD.** A comprehensive study performed in Switzerland identified the most important risk factors *(Picco et al., 2008)*.



The clinical presentation is characterised by intense pruritus, occasionally even prior to the appearance of the first lesions, as well as erythema, maculae and papules on the face, inner surface of the ears, ventral neck, axillae, groin, abdomen, perineum, ventral surface of the tail, flexion regions of the limbs and interdigital spaces. Obviously, not all the body regions mentioned above are affected in all animals.

As the process progresses and becomes chronic, hypertrichosis (due to scratching), hyperpigmentation and, finally, lichenification develop in the erythematous patches. Animals affected with CAD often present bilateral otitis externa, bilateral conjunctivitis or secondary bacterial (bacterial folliculitis) or yeast infections (*Malassezia* overgrowth).

The diagnosis of CAD is clinical. Firstly, it is essential to rule out pruritic parasitic (sarcoptic scabies, demodicosis, fleas) and infectious diseases (bacterial folliculitis, *Malassezia* overgrowth). In all cases, rigorous control of flea infestations should be initiated to rule out an allergy to flea saliva. A possible food allergy or intolerance should then be ruled out. To that end, the patient is fed exclusively with a specific diet for 8 weeks. Two alternative diets can be used: home-made diets based on potatoes and a protein source that the patient has not eaten before (meat from previously unconsumed species such as horse, rabbit, goat, kangaroo, etc.) and diets based on hydrolysed proteins (Advance Hypoallergenic) (*Olivry & Bizikova, 2010*). If no improvement is noted after 8 weeks, a food allergy can be ruled out as the cause of the patient's problem. If, in contrast, the patient exhibits a marked improvement (greater than 50% reduction in pruritus), a challenge test should be carried out to confirm the improvement is diet-related. This is done by giving the dog the initial diet again. If the pruritic dermatitis reappears, it confirms the diagnosis of a food allergy (adverse food reaction). However, if the clinical signs are still absent 2 weeks after returning to the original diet, the improvement is not the result of the change in diet and therefore a food allergy can be ruled out as the cause of the dog's dermatitis.



Once parasites, pyoderma (bacterial folliculitis) and food allergies have been ruled out, a diagnosis of CAD can be established, so long as the clinical signs are compatible. As such, this clinical diagnosis is reached when the clinical signs and history are compatible and after ruling out other causes of pruritus.

The diagnosis of CAD is clinical. It is established in an animal with a compatible clinical presentation and history and in which other common causes of pruritus, such as sarcoptic scabies, demodicosis, bacterial folliculitis, *Malassezia*-related dermatitis and food allergies have been ruled out.

3. TREATMENT

It is particularly important to explain to the animal's owners that, as CAD is a disease with a marked genetic component, treatment must be followed to a varying degree throughout the animal's entire life. There is no "cure" for this disease, and therapeutic measures and lifestyle changes that significantly improve the animal's clinical presentation are the only solution (*Olivry et al., 2010*).

Control measures can be divided into general supportive measures, which are highly recommended in all atopic animals, and specific therapeutic interventions. Although supportive measures are generally unable to control the most severe cases of CAD, they can nevertheless help facilitate management and mean the dose of the drugs with the strongest side effects (such as corticosteroids) can be reduced. In other words, although they cannot control the disease on their own, but the disease is much harder to treat without them. The three most important measures are:

a) Strict control over ectoparasites.
b) Frequent baths with a suitable shampoo.
c) A specific diet for atopic dogs.

Atopic dogs should be constantly treated to eliminate endo- and ectoparasites given that the presence of parasites (especially fleas) worsens the clinical signs of atopic dermatitis. Frequent baths (1–3 times per week, depending on the animal) help control secondary infections (staphylococci, yeasts), eliminate allergens from the surface of the skin and may have anti-inflammatory or antipruritic effects (depending on the shampoo).

A suitable diet for atopic dogs, which is an essential component of the control program, is discussed in greater detail in section 4. In all cases of CAD, irrespective of the specific therapy applied, it is essential that these supportive measures are followed strictly, regularly and throughout the dog's lifetime.

Fortunately, there are currently numerous options available for the treatment of CAD, including allergen-specific immunotherapy, corticosteroid therapy (topical or systemic), cyclosporin A, oclacitinib or the anti-IL-31 monoclonal antibody (lokivetmab). There is no standard treatment for all cases. A specific treatment must be designed for each atopic patient based on the following points:

- Patient characteristics (age, history, etc.)
- CAD characteristics (inflammation, otitis, etc.)
- Seasonality
- Severity and distribution of the lesions and pruritus
- Presence of secondary infections

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CAD treatment is multimodal, so there are various therapeutic targets (inflammatory reaction, hypersensitivity reaction, immune response, pruritus and epidermal barrier), different routes of administration and even the inclusion of hygiene/dietary habits (adapted diet, baths, prevention of endo- and ectoparasites).

Table 1. CAD control measures.

Treatment of the OUTBREAK	LONG-TERM management
SPECIFIC TREATMENT	
• Oclacitinib • Prednisone/prednisolone • Control of secondary infections	• Cyclosporin • Allergen-specific immunotherapy
SUPPORT THERAPY	
adapted **DIET** (antigen limitation, EFAs*)	**FREQUENT BATHS** with a suitable shampoo
CONTROL of ecto- and endoparasites	

*EFAs: essential fatty acids.

Fortunately, there are currently numerous options available for treating CAD, including allergen-specific immunotherapy, corticosteroid therapy (topical or systemic), cyclosporin A, oclacitinib or the anti-IL-31 monoclonal antibody (lokivetmab).

Clinical practice guidelines distinguish between treatment of the acute and chronic phases (Table 1). During the acute phase it is important to prevent ectoparasites, control secondary infections and act rapidly to control pruritus and inflammation. The drugs indicated for rapid control of pruritus include oclacitinib, lokivetmab and corticosteroids at anti-inflammatory doses. In addition, it is important to initiate a regimen of baths every 2-4 days with a suitable shampoo if the dog has an infections, and administer treatment to control the pruritus and inflammation. Treatment of the acute phase normally lasts 3-4 weeks.

The chronic phase treatment should then be initiated, which is intended to prevent or at least reduce the severity of relapses or outbreaks of allergy.

In addition to support therapy, the vet must now decide whether to use allergen-specific immunotherapy or one of the indicated drugs.

Given their side-effects, glucocorticoids are not recommended for the long-term treatment of CAD.

Allergen-specific immunotherapy is performed after identifying the responsible allergens using an *in vivo* (intradermal) or *in vitro* test (determination of IgEs in serum). Given there are practically no side effects, immunotherapy appears to be the ideal option. However, the main disadvantage is its limited efficacy: it is only effective in around 60% of cases (this value varies between 40% and 80%, depending on the study). If one of the drug therapies is chosen, there is no need to identify the causative allergens. As mentioned above, there is no ideal drug that is effective in all cases. Each drug option has its own advantages and disadvantages, and the vet must decide which is the most appropriate for each patient.

4. THE ROLE OF DIET IN CAD CONTROL

Nutritional support treatment for atopic dermatitis is based on:

4.1. Improving skin barrier function.
4.2. Reducing the allergic inflammatory response and pruritus.
4.3. Stimulating skin healing.
4.4. Restricting allergens in the diet.

4.1. IMPROVING SKIN BARRIER FUNCTION

The skin barrier relies on the outermost layer of the skin, called the stratum corneum, which comprises corneocytes embedded in a lipid matrix.

These lipids are mainly ceramides, cholesterol and free fatty acids. Atopic dermatitis can affect the total quantity of lipids in the stratum corneum or their relative concentrations, increasing skin dehydration and the penetration of skin allergens.

Various studies have suggested that different nutrients can strengthen the skin barrier.

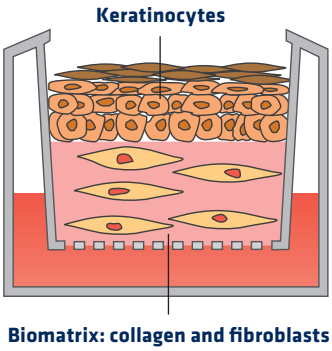
To study the effects of various compounds on the canine skin barrier, Affinity's research department has promoted the **development of an artificial canine skin model** (*Serra et al., 2007*) to facilitate these studies without having to harm any animals by performing skin biopsies (Figure 4). We used this model to compare the lipid composition of the canine epidermis with that of other species and with artificial canine skin (Table 2), while also examining the effect of the oral administration of various functional ingredients on skin health.

4.1.1. Aloe gel: effect of oral supplements on the canine skin barrier.

Aloe vera (*Aloe barbadensis millar*) is a plant from the cactus family that has been used for medicinal purposes by the Egyptian, Indian and Chinese cultures for over 5000 years. Aloe gel (or mucilage) is a clear, viscous liquid extracted from the central part of the fleshy leaves of the aloe plant and used to treat digestive disorders, skin diseases and to heal wounds. The gel contains water and a small quantity of solids, basically mannose-containing polysaccharides (mannans) and other compounds such as vitamins, minerals, enzymes, phenolic compounds and organic acids. When aloe gel is ingested, the intestinal bacteria convert the mannans into substances with a lower molecular weight that can be partially absorbed (*Yagi et al., 2001*). The biological activity of aloe is due to polysaccharides with a molecular weight of between 50,000 and 100,000 Daltons.

Aloe gel is one of the compounds that has shown a marked activity in the stimulation of the skin barrier in the artificial canine skin model. Figure 5 shows the effect of aloe gel on the quantity of lipids in synthetic canine skin.

Figure 4. Artificial canine skin model used in different studies.



Serra et al. (2007) Experimental Dermatology 2007, 16: 135-142.

4.1.2. Effect of supplementation with omega-6 (n-6) essential fatty acids (EFAs) on the canine skin barrier.

Supplementing dogs' diets with omega-6 EFAs ensures cohesion of the epidermis, helps maintain the skin barrier hydrated and provides precursors of the eicosanoids and other components and mediators of cell function. In healthy skin, ceramides, which contain n-6 linoleic acid (LA), are secreted by keratinocytes in the epidermis into the intercellular space to ensure cellular cohesion and the efficacy of the skin barrier. Several authors have highlighted the importance of linoleic acid levels on canine skin health, such as *Rees et al. (2001)*, who observed a significant improvement in the appearance of canine skin and hair after supplementation with LA-rich oils, *while Marsh et al. (2000) reported a decrease in skin dehydration*. According to *Kirby et al. (2009)*, in veterinary practice it is advisable to wait a period of 6-8 weeks after supplementation with any type of fatty acid before assessing any improvement in skin and hair quality. According to a study by *Seavik et al. (2002)*, the level of linoleic acid found in the serum of atopic dogs was significantly lower than in their healthy counterparts, as can be seen from Table 3.

Table 2. Epidermal lipids in different species and the artificial canine skin model. Internal data.

	EPIDERMIS			ARTIFICIAL SKIN
	Human	Porcine	Canine	Canine
% Total lipids	19.3	15.2	11.65	17.6
% Free *FA	33.25	22.64	47.2	38.22
% Cholesterol	33.28	36.15	21.68	30.72
% Polar lipids	33.47	41.2	35.45	30.73

*FA: fatty acids

Atopic dermatitis is related to changes in the organisation of lipids in the stratum corneum, and various studies have reported reduced levels of linoleic (n-6) and alpha-linoleic acid (n-3) metabolites, which was attributed to a deficit in Δ5 and Δ6 desaturase enzyme activity in the epidermis (*Schlotter et al., 2009*).

4.2. REDUCING THE ALLERGIC INFLAMMATORY RESPONSE AND PRURITUS

4.2.1. Effect of supplementation with omega-3 essential fatty acids (EFAs)

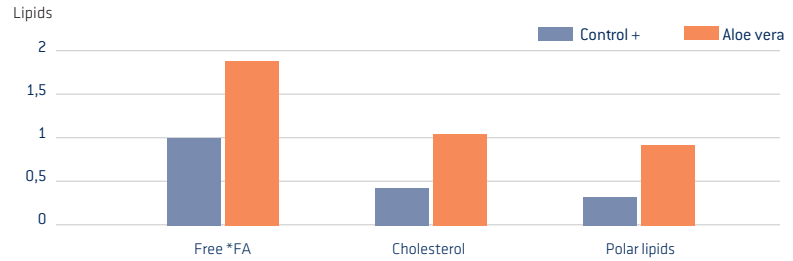
Supplementation with EFAs was proposed as a treatment for canine atopic dermatitis in the mid-1980s. It is thought that approximately 20% of dogs with allergic pruritus can be controlled by supplementation with essential fatty acids (*Scott et al., 2001*). It has also been shown that the effect of supplementation with essential fatty acids (linoleic acid (LA), α-linolenic acid (ALA), eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA)) allows a reduction in glucocorticoid dose during long-term treatment, although an induction period is required (30-40 days) before the effect is notable (Saevik et al., 2004), as shown in Figure 6.

The influence of polyunsaturated fatty acids (PUFAs) on the immune response is increasingly being recognised in both human and veterinary medicine. In an in vitro study, *Stehle et al. (2010)* observed a decline in the proliferation of lymphocytes from atopic dogs when incubated with PUFAs (α-linolenic, EPA and DHA), which may contribute to the clinical effects of this supplement.

4.2.2. Effect of supplementation with olive leaf extract.

Traditional medicine is based on exploiting the curative properties of numerous compounds biosynthesised and stored in the leaves, fruits and roots of a wide range of plants. Historically, olive derivatives have been used as skin emollients, tonics and sedatives.

Figure 5. Effect of aloe vera gel supplementation on artificial canine skin cultures in terms of total composition of the main lipids in the canine epidermis and dermis. (Internal data)



*FA: fatty acids

Figure 6. Dose of prednisolone received by EFA (LA, alpha-LA, EPA and DHA)-supplemented group and placebo group. *Saevik et al., (2004).*

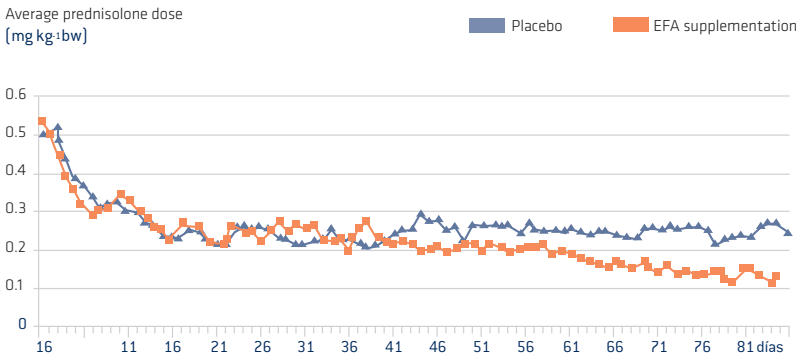


Figure 7. Effect of oral supplementation with olive leaf extract on cytokine secretion in splenocytes with chronic inflammation (adapted from *Cvjeticanin et al., 2010*)

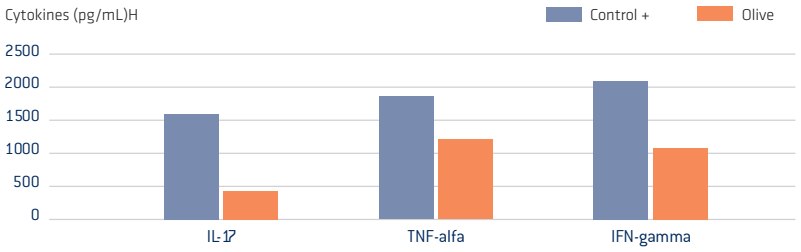


Table 3. Fatty acid composition of sera from healthy and atopic dogs (Seavik *et al.*, 2002).

	Healthy dogs	Atopic dogs
Palmitic acid %	16.1*	15.1*
Oleic acid %	11.6	12.1
Total Omega 6 mg/ml	28.1*	25.9*
Total Omega 3 mg/ml	2.03	1.71
Total saturates mg/ml	2.3*	3.31*

* p<0.05

Indeed, olive leaf extract is known to be very rich in compounds with a wide range of activities. These compounds are mainly oleuropeosides (23-30%, mainly oleuropeine, verbascoside and hydroxytyrosol) and flavones (2-4.5%, luteolin and apigenin glycosides), some of which have demonstrated antimicrobial (viruses, bacteria, yeasts, parasites and fungi), antioxidant (Benevente-García et al., 2000), and anti-inflammatory activity (Figure 7).

Upon analysing their antimicrobial activity, Sudjana et al. (2009) highlighted that olive leaf extract is a more potent inhibitor of Staphylococcus aureus growth (including methicillin-resistant strains (MRSA)) even at inhibitory concentrations as low as 0.3-0.78% v/v.

Acute or chronic inflammation generates a large quantity of free radicals which accelerate the inflammatory process by oxidising the proteins and lipids in tissues. **The marked antioxidant capacity of olive leaf extract slows propagation of the oxidative cycle and inflammatory process.**

4.3. STIMULATING SKIN HEALING

Collagen is the main component of the extracellular matrix in conjunctive tissue. This protein is secreted by cells in the connective tissue, such as fibroblasts, and is the most abundant component of the skin. Collagen is characteristically very rich in certain amino acids, namely proline, hydroxyproline and glycine. Some authors have shown that millimolar concentrations of collagen peptides have an attractive and proliferative action on fibroblasts that may result in improved healing and less inflammation.

4.4. RESTRICTION OF DIETARY ALLERGENS

In 2008, and in light of evidence that dietary allergens can also trigger episodes of dermatitis in atopic animals, the **International Task Force on Canine Atopic Dermatitis recommended a reduction in dietary allergens as a first step in management of CAD** *(Olivry et al 2010)*. Thus, dogs suffering from atopic dermatitis should be fed with alternative sources of protein to those commonly found in their diet, such as trout, mink, kangaroo or rabbit proteins. ■

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