

Natural Product Research

Formerly Natural Product Letters




ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: <http://www.tandfonline.com/loi/gnpl20>

Lactoferricin/verbascoside topical emulsion: a possible alternative treatment for atopic dermatitis in dogs

Elena Biasibetti, Natascia Bruni, Mauro Bigliati & Maria Teresa Capucchio

To cite this article: Elena Biasibetti, Natascia Bruni, Mauro Bigliati & Maria Teresa Capucchio (2017): Lactoferricin/verbascoside topical emulsion: a possible alternative treatment for atopic dermatitis in dogs, Natural Product Research

To link to this article: <http://dx.doi.org/10.1080/14786419.2017.1365066>

 View supplementary material  Published online: 28 Aug 2017. Submit your article to this journal  View related articles  View Crossmark data 

SHORT COMMUNICATION



Lactoferricin/verbascoside topical emulsion: a possible alternative treatment for atopic dermatitis in dogs

Elena Biasibetti^a, Natascia Bruni^b, Mauro Bigliati^c and Maria Teresa Capucchio^a

^aDepartment of Veterinary Science, University of Turin, Grugliasco, Italy; ^bCandioli Farmaceutici S.p.A., Beinasco, Italy; ^cAmbulatorio Vernazza, Torino, Italy

ABSTRACT

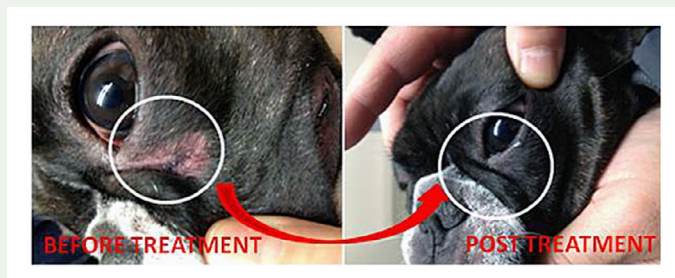
Atopic dermatitis affects 3–15% of the general dog population and it has been diagnosed by veterinarians up to 58% of dogs affected with skin disease. It is usually a life-long pathology which can be controlled, but it can be seldom cured. The present investigation describes a case study in which lactoferricin and verbascoside are part of a formulation to obtain a dermatological lotion for canine dermatitis treatment. The study was an open-label trial design of two-week treatment. Thirty-eight dogs (23 females and 15 males), with atopic dermatitis and secondary bacterial or yeast overgrowth have been included. During treatment period the total clinical score progressively decreased associated with an improvement in clinical signs. No adverse effects were reported in any of the treated dogs. The present research suggests that daily applications of tested emulsion are effective in reducing bacterial overgrowth and clinical signs in skin folds and atopic dermatitis.

ARTICLE HISTORY

Received 3 April 2017
Accepted 28 July 2017

KEYWORDS


Lactoferricin; verbascoside; dog; atopic dermatitis



1. Introduction

Atopic dermatitis (AD) affects 3–15% of the general dog population and it has been diagnosed by veterinarians up to 58% of dogs affected with skin disease (Hillier and Griffin 2001; Hill et al. 2006). It is usually a life-long pathology which can be controlled, but it can be seldom cured. It can be done on the basis of the most important clinical features, which include pruritus associated with skin lesions, especially around the mouth, eyes, ears, elbow, carpal and tarsal joints, digits, ventral abdomen and proximal region of tail (Marsella et al. 2013).

CONTACT Elena Biasibetti ✉ elena.biasibetti@unito.it

 Supplemental data for this article can be accessed at <https://doi.org/10.1080/14786419.2017.1365066>.

© 2017 Informa UK Limited, trading as Taylor & Francis Group

Medicinal plants have been used as alternative treatments to improve skin inflammation, it has been possible to develop newer and more potent topical and/or injectable drugs to treat inflammatory skin complications (Kim et al. 2016; Maione et al. 2016). Some of them are used as remedy for their anti-inflammatory and/or antiseptic activity. Mixtures of essential oils from Mediterranean plants were tested as alternative approach for the management of canine Malassezia otitis (Nardoni et al. 2016).

Canine AD is often associated/caused to/by bacterial (mainly staphylococcus) (Bradley et al. 2016; Saridomichelakis and Olivry 2016) and fungal or yeast infection (mainly Malassezia pachydermatis) (Saridomichelakis and Olivry 2016) of the damaged region, which are also responsible of most of symptoms. Thus, antibiotic local treatment could represent an effective route to reduce the most relevant symptoms and to limit the skin infection. Among all antibiotic agents lactoferricin is a natural antimicrobial peptide which shows a wide range of activity against bacterial, fungal, viral and parasitic pathogens (Gonzalez-Chavez et al. 2009; Vogel 2012). Natural products are a significant source of novel antimicrobial compounds, and an increasing number are being identified from mammalian sources, including milk proteins. One example is the multifunctional iron-binding glycoprotein, lactoferrin and its various derived peptides. This behaviour could be explained comparing the structure of intact protein with structure of lactoferricin peptide, which was determined by Hwang et al. in 1998 by NMR spectroscopy (Hwang et al. 1998). The antibacterial activity of lactoferricin is thought to involve the disordering and alteration of the permeability of the bacterial membrane, resulting in inhibition of macromolecular biosynthesis and ultimately cell death (Ulvatne et al. 2001).

Due to the above-described features, lactoferricin is a promising candidate as antimicrobial agent for local treatment of canine dermatitis. The present investigation describes a case study in which lactoferricin is part of a formulation, together with verbascoside (a caffeoyl phenylethanoid glycoside) and glycerophosphoinositol lysine (a sunflower lecithin-derived) to obtain a dermatological lotion for canine dermatitis treatment.

2. Results and discussion

The stability of the preparation was carried out on three different batches. The evaluation of microbial contamination, carried out at the expiration of the observation period, shows that the defined microbiological requirements are respected after 36 months of storage at room temperature.

On the basis of the observed data, it is possible to conclude that the prepared lotion has good long-term conservation stability at room temperature, without any significant alterations in terms of organoleptic and physico-chemical properties and active principle titration.

During the first examination, veterinarians assigned to 21 dogs showed a CADESI score 3, to nine dogs a score 4 and to eight dogs a score 2. After 15 days from the first application of the lotion the score showed a significant reduction: the majority of dogs treated showed a CADESI score 1 (29 cases), five dogs had a score 0 and four dogs a score 2. Also lichenification and alopecia reported a significant reduction; excoriation showed a negative trend. A significant decrease was also reported in the Pruritus VAS. In cytological smears, the efficacy of the product was evaluated determining the number of corneocytes, parameter of desquamation and so of the epidermal integrity. A significant decreasing in the number of corneocytes was observed reducing the desquamation process.

It has been recently demonstrated that some bacteria are responsible to trigger inflammatory response, in AD region, by exploiting the epidermal barrier defect (Nakatsuji et al. 2016). In our study after two weeks of treatment, bacteria were significantly reduced. Moreover, despite the yeasts did not have a significant reduction, the score showed a reduction in most animals ($n^{\circ}31$). Lactoferricin represents probably the active ingredient of our formulation with antimicrobial activity. This activity could be related to membrane disturbing effects, i.e. membrane permeabilisation and depolarisation (Sijbrandij et al. 2017). In fact on Gram-negative bacteria, this peptide acts on lipopolysaccharides, whereas on Gram-positive bacteria lactoferricin acts on lipoteichoic and teichoic acids (Bruni et al. 2016).

The primary antifungal mechanism of action of lactoferricin appears to be through direct interaction with the fungal surface and disruption of the fungal membrane (Bellamy et al. 1992).

The damage due to skin inflammation can be improved for the presence in the lotion of verbascoside too, a phenylpropanoid glycoside known for its antioxidant, anti-inflammatory and photoprotective actions. In particular a precedent study demonstrated that verbascoside promotes skin repair and ameliorates skin inflammation due to its ROS scavenging, antioxidant, iron chelating and glutathione transferase (GST) activity-inducing properties (Vertuani et al. 2011).

The antibacterial and anti-inflammatory activity of verbascoside could be correlated with the reduction of clinical symptoms and consequently the dermatological score.

In conclusion, during the two-week treatment period the total clinical score progressively decreased with an improvement in clinical signs. No adverse effects were reported in any of the treated dogs. The present research, even if it was an uncontrolled study performed on a small number of dogs, suggests that daily applications of the tested emulsion are effective in reducing bacterial overgrowth and clinical signs in skin folds and AD.

3. Experiment

See supplementary materials for data collection and statistical analysis.

Acknowledgements

The authors would like to thank Luisa Cornegliani and Antonella Vercelli for the photos of graphical abstract.

Disclosure statement

One of the authors, Natascia Bruni, is an employee of Candioli Farmaceutici S.p.A., a company that may be affected by the research reported. This interest has been fully disclosed to Taylor & Francis.

References

- Bellamy W, Takase M, Yamauchi K, Wakabayashi H, Kawase K, Tomita M. 1992. Identification of the bactericidal domain of lactoferrin. *Biochim Biophys Acta*. 1121:130–136.
- Bradley CW, Morris DO, Rankin SC, Cain CL, Misic AM, Houser T, Mauldin EA, Grice EA. 2016. Longitudinal evaluation of the skin microbiome and association with microenvironment and treatment in canine atopic dermatitis. *J Invest Dermatol*. 136:1182–1190.

- Bruni N, Capucchio MT, Biasibetti E, Pessione E, Cirrincione S, Giraudo L, Corona A, Dosio F. [2016](#). Antimicrobial activity of lactoferrin-related peptides and applications in human and veterinary medicine. *Molecules*. 21(6). pii: E752.
- Gonzalez-Chavez SA, Arevalo-Gallegos S, Rascon-Cruz Q. [2009](#). Lactoferrin: structure, function and applications. *Int J Antimicrob Agents*. 33(301):e1–8.
- Hill PB, Lo A, Eden CA, Huntley S, Morey V, Ramsey S, Richardson C, Smith DJ, Sutton C, Taylor MD, et al. [2006](#). Survey of the prevalence, diagnosis and treatment of dermatological conditions in small animals in general practice. *Vet Rec*. 158:533–539.
- Hillier A, Griffin CE. [2001](#). The ACVD task force on canine atopic dermatitis (I): incidence and prevalence. *Vet Immunol Immunopathol*. 81:147–151.
- Hwang PM, Zhou N, Shan X, Arrowsmith CH, Vogel HJ. [1998](#). Three-dimensional solution structure of lactoferricin B, an antimicrobial peptide derived from bovine lactoferrin. *Biochemistry*. 37:4288–4298.
- Kim TW, Choi JM, Kim MS, Son HY, Lim JH. [2016](#). Topical application of *Scutellaria baicalensis* suppresses 2,4-dinitrochlorobenzene-induced contact dermatitis. *Nat Prod Res*. 30:705–709.
- Maione F, Russo R, Khan H, Mascolo N. [2016](#). Medicinal plants with anti-inflammatory activities. *Nat Prod Res*. 30:1343–1352.
- Marsella R, Atopic disease, Miller WHJ, Griffin CE, Campbell KL, editors. [2013](#). Muller & Kirk's small animal dermatology. 7th ed. St. Louis (MO): Elsevier Mosby; p. 365–388.
- Nakatsuji T, Chen TH, Two AM, Chun KA, Narala S, Geha RS, Hata TR, Gallo RL. [2016](#). *Staphylococcus aureus* exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. *J Invest Dermatol*. 136:2192–2200.
- Nardoni S, Pistelli L, Baronti I, Najar B, Pisseri F, Bandeira Reidel RV, Papini R, Perrucci S, Mancianti F. [2016](#). Traditional Mediterranean plants: characterization and use of an essential oils mixture to treat Malassezia otitis externa in atopic dogs. *Nat Prod Res*. 5:1–4.
- Saridomichelakis MN, Olivry T. [2016](#). An update on the treatment of canine atopic dermatitis. *Veterinary J*. 207:29–37.
- Sijbrandij T, Ligtenberg AJ, Nazmi K, Veerman EC, Bolscher JG, Bikker FJ. [2017](#). Effects of lactoferrin derived peptides on simulants of biological warfare agents. *World J Microbiol Biotechnol*. 33:160.
- Ulvatne H, Haukland HH, Olsvik Ø, Vorland LH. [2001](#). Lactoferricin B causes depolarization of the cytoplasmic membrane of *Escherichia coli* ATCC 25922 and fusion of negatively charged liposomes. *FEBS Lett*. 492:62–65.
- Vertuani S, Beghelli E, Scalambra E, Malisardi G, Copetti S, Toso R, Baldisserotto A, Manfredini S. [2011](#). Activity and stability studies of verbascoside, a novel antioxidant, in dermo-cosmetic and pharmaceutical topical formulations. *Molecules*. 16:7068–7080.
- Vogel HJ. [2012](#). Lactoferrin, a bird's eye view. *Biochem Cell Biol*. 90:233–244.