Vet Res Commun
DOI 10.1007/s11259-015-9651-4

ORIGINAL ARTICLE

Clinical evaluation of an antiinflammatory and antioxidant diet effect in 30 dogs affected by chronic otitis externa: preliminary results

Alessandro Di Cerbo[1] · Sara Centenaro[2] · Francesca Beribè[3] · Fulvio Laus[3] · Matteo Cerquetella[3] · Andrea Spaterna[3] · Gianandrea Guidetti[2] · Sergio Canello[2] · Giuseppe Terrazzano[4,5]

Received: 16 July 2015 / Accepted: 21 December 2015

Abstract The aim of this evaluation study was to assess the possible role of a specific nutraceutical diet in relieving main clinical symptoms of chronic bilateral otitis externa (occlusion of ear canal, erythema, discharge quantity, and odor) in 30 adult dogs. Thirty dogs of different breeds (mean age ± SEM; 6.03 ± 0.15 years and mean weight ± SEM; 32.01 ± 1.17 Kg; 53.3 % males, 46.6 % females) with evident chronic clinical otitis symptoms were equally divided and randomly assigned to receive either the nutraceutical diet (ND group) or a standard diet (SD group) over a period of 90 days. In all cases a topical pharmacological treatment was given. The nutraceutical diet, also endowed with anti-inflammatory and antioxidant activities, significantly decreased the mean score intensity of all symptoms after 90 days of intervention ($P < 0.0001$) with the exception of *Malassezia pachydermatis* infection which was only slightly reduced. Our investigation is one of the few evidence-based results where a commercial nutraceutical diet has been proven effective, in combination with drugs, in relieving otitis externa-related symptoms. This study opens new insights into otitis externa clinical management providing evidence of efficacy of a combined therapy with drugs and a specific nutraceutical diet.

Keywords Nutraceutical diet · Otitis externa · Symptoms intensity decrease · Antiinflammatory and antioxidant activities

Alessandro Di Cerbo and Sara Centenaro contributed equally to this work.

✉ Alessandro Di Cerbo
alessandro811@hotmail.it

Sara Centenaro
Sarac.sanypet@forza10.com

Francesca Beribè
francesca.beribe@unicam.it

Fulvio Laus
fulvio.laus@unicam.it

Matteo Cerquetella
matteo.cerquetella@unicam.it

Andrea Spaterna
andrea.spaterna@unicam.it

Gianandrea Guidetti
Gianandrea.sanypet@forza10.com

Sergio Canello
Sergio.sanypet@forza10.com

Giuseppe Terrazzano
giuseppe.terrazzano@unibas.it

[1] School of Specialization in Clinical Biochemistry, "G. d'Annunzio" University, Chieti, Italy

[2] Research and Development Department, SANYpet S.p.a., Bagnoli di Sopra, Padua, Italy

[3] School of Biosciences and Veterinary Medicine, University of Camerino, Camerino, Italy

[4] Department of Science, University of Basilicata, Potenza, Italy

[5] Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy

Published online: 07 January 2016

Text

Otitis externa is supposed to affect 4 out of 1,000 persons annually in USA (Osguthorpe and Nielsen 2006). Its chronic expression affects 3–5 % of the same population (Agius et al. 1992; Daneshrad et al. 2002; Hannley et al. 2000; Sood et al. 2002) whereas the acute one is unilateral in 90 % of cases and affects 7 to 12 years aged people declining after 50 years. Further, the acute otitis externa is often associated with local trauma, hearing aids, swimming, warmer temperatures, high humidity and hearing protector use (Beers and Abramo 2004). Otitis externa is commonly due to bacterial or occasionally fungal infections (Sander 2001) following an increased ceruminal pH level (Halpern et al. 1999), which enhances the microbial growth (Beers and Abramo 2004; Daneshrad et al. 2002; Sander 2001; Tsikoudas et al. 2002), and/or an insufficient amount of earwax (Beers and Abramo 2004; Sander 2001). Early clinical symptoms are pruritus, erythema and pain. As the disease proceeds, the erythema increases and is followed by edema and otorrhea. If untreated, the pain becomes intense, the lumen of the ear canal gets obstructed and the conductive hearing loss might occur (Beers and Abramo 2004; Daneshrad et al. 2002; Sander 2001).

Otitis externa is also one of the more frustrating disease affecting pets (Pietschmann et al. 2013). Its clinical evolution can be summarized in three phases: 1) acute inflammation and edema, 2) chronic inflammation (glandular changes, fibrosis and scarring) and 3) progressive stenosis and occlusion of the ear canal (Logas 1994; Roth 1988). Calcification and even ossification of cartilage might also occur as well as otitis media and aural cholesteatoma (Logas 1994). Chronic processes, as a consequence, enhance bacteria moltiplication, such as *Pseudomonas spp,* with secondly induced lesions (McKeever and Torres 1997; Roth 1988). It is generally recognized that cleaning and drying the ear canal can reduce inflammation and resolve secondary infections (Rosychuk 1994). However, antimicrobials (Polimixin B, Enrofloxacin, Orbifloxacina, rifaximin, Gentamicin, etc.) and antimycotics (Miconazole, Clotrimazole, Posaconazole, etc.) remain the gold standard against most of pathogens (*Staphylococcus spp, Pseudomonas aeruginosa, Escherichia coli*, *Proteus mirabilis* and *Malassezia pachydermatis*) (Engelen et al. 2010; Engelen and Anthonissens 2000; Peano et al. 2012; Rougier et al. 2005; Studdert and Hughes 1991). *Malassezia pachydermatis* has been identified as the most common yeast organism present in ears of dogs affected by otitis externa (Cole et al. 2007; Crespo et al. 2002). This yeast colonizes the ear canal surface and is usually found adherent to clumps of exfoliated squamous epithelial cells (Porter 2011). It can be rapidly identified by microscopic examination and normally should not exceed 10 organisms per high-power field (Cowell et al. 2008).

The aim of this clinical evaluation was to observe the effect of a commercial nutraceutical diet, also endowed with anti-inflammatory and antioxidant activities, as an adjuvant in pharmacological treatment of dogs affected by chronic otitis externa in order to improve the intensity of its clinical signs as well as the presence of *Malassezia pachydermatis*. The antiinflammatory and antioxidant activities of the proposed diet have to ascribed to the presence of the pool of fish hydrolyzed proteins, rice carbohydrates, *Melaleuca alternifolia, Tilia cordata, Allium sativum L, Rosa canina L.,* Zinc and a well balanced Omega3:6 ratio (1:0.8).

In this regard, Tea tree oil (TTO) of *Melaleuca alternifolia* has been widely used as antimicrobial (Carson et al. 2006; Mikus et al. 2000) and anti-inflammatory phytotherapic coumpound [(reduction of Tumor necrosis factor-α, Interferon-γ, Interleukin-2] (Baldissera et al. 2014) for the presence of terpinen-4-ol and 1.8-cineole (Caldefie-Chezet et al. 2006; Dalwai et al. 2014; de Campos Rasteiro et al. 2014; Furneri et al. 2006; Greay et al. 2010; Hammer 2015; Ireland et al. 2012; Mantil et al. 2015; Nogueira et al. 2014). TTO is also known to exert antioxidant effects on human peripheral blood mononuclear cells by reducing reactive oxigen species production and IL-2 secretion in T lymphocytes, and increasing the secretion of the anti-inflammatory cytokines such as Interleukin-4 and Interleukin-10 (Caldefie-Chezet et al. 2006). Several human studies have also evidenced the benificial effect of TTO in experimentally induced skin reactions (nickel- or histamine-induced contact hypersensitivity) (Khalil et al. 2004; Koh et al. 2002; Pearce et al. 2005; Wallengren 2011).

Anti-inflammatory and antioxidant activities have been also ascribed to flowers, bracts and leaves of *Tilia cordata,* usually known as lime tree (Russo et al. 2000; Scherl et al. 2012; Toker et al. 2001). Antioxidant (Banerjee et al. 2001, 2002; Fanelli et al. 1998; Lau 2001; Lin et al. 1996; Maslin et al. 1997; Prasad et al. 1996), antimicrobial (Dini et al. 2011; Jonkers et al. 1999; Karuppiah and Rajaram 2012; Wills 1956), anti-protozoal (An et al. 2009; Perez et al. 1994; Watson 1996), antifungal (Adetumbi et al. 1986; Ghannoum 1988; Shams-Ghahfarokhi et al. 2006; Szymona 1952), antiviral (Guo et al. 1993; Tsai et al. 1985; Weber et al. 1992), hypotensive (Chaupis-Meza et al. 2014; Majewski 2014; Rashid and Khan 1985; Reinhart et al. 2008; Ried et al. 2010; Sobenin et al. 2009; Stabler et al. 2012), cardioprotective (Allison et al. 2012; Ashraf et al. 2013; Bordia et al. 1998; Sumiyoshi and Wargovich 1990) and anti-tumor (Amagase and Milner 1993; Capasso 2013; Lin et al. 2002; Sumiyoshi and Wargovich 1990; Tadi et al. 1991a, b; Tsubura et al. 2011; Wallace et al. 2013; Wang et al. 2012) effects were observed for *Allium sativum L.,* commonly known as garlic, due to the presence of biologically active substances such as allicin, ajoene and diallyl trisulfide. *Rosa canina L.* is a plant whose berries are endowed with antioxidant, anti-inflammatory, immunomodulating and

antimicrobial activity due to the presence of phenolic acids, proanthocyanidins, tannins, flavonoids, unsaturated and polyunsaturated fatty acids, phospholipids, minerals, galactolipids, carotenoids and triterpenes (Chrubasik et al. 2008; Sadigh-Eteghad et al. 2011). This plant exerts a specific anti-inflammatory activity (Jager et al. 2007, 2008; Larsen et al. 2003; Lattanzio et al. 2011; Wenzig et al. 2008), some immunomodulatory and antioxidant activities (Davitashvili et al. 2010; Sadigh-Eteghad et al. 2011; Sies et al. 1992; Takashima et al. 2012; Tumbas et al. 2012), and antimicrobial effects (Shiota et al. 2000). Additional activities ascribed to this plant are antiulcerogenic and probiotic (Deliorman Orhan et al. 2007; Gurbuz et al. 2003; Johansson et al. 1998), hypoglycemic (Ninomiya et al. 2007), antimutagenic and anticancerogenic (Trovato et al. 1996).

Immunomodulatory activities have also been ascribed to zinc, whose deficiency affects innate and adaptive immunity, exacerbates inflammation (Bonaventura et al. 2014) and is closely related to skin desease and wound healing (Colombini 1999) since its absolute or relative deficiency can cause the onset of canine zinc-responsive dermatosis (Hensel 2010).

An optimal balance of the omega 3:6 fatty acids ratio in the food is considered a fundamental requirement for tissue to improve homeostasis and contrast the inflammatory processes. More in details, n-3 polyunsaturated fatty acids, usually found in fish oil, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known to decrease the production of proinflammatory mediators and inhibit natural killer cell activity (Kelley et al. 1999). In addition, the n-6 polyunsaturated fatty acid gamma-linolenic acid (GLA) and EPA are endowed with specific antiinflammatory activity (DeLuca et al. 1999).

Based on such considerations, we performed a randomized placebo-controlled clinical evaluation on 30 dogs with evident chronic clinical otitis symptoms such as occlusion of ear canal, erythema, discharge quantity, and odor.

Materials and methods

The animals

Thirty adult dogs of different breeds (mean age ± SEM; 6.03 ± 0.15 years and mean weight ± SEM; 32.01 ± 1.17 Kg; 53.3 % males, 46.6 % females) with evident chronic clinical otitis symptoms were randomly divided and assigned to receive either the specific diet (treatment group, $n = 15$) or the placebo (control group, $n = 15$) once a day for 90 days, accordingly with the following manifacture's table (Table 1). In addition, all dogs were also pharmacologically treated with a topic product (OTOMAX, Schering-Plough, Kenilworth, NJ, USA) 8 drops a day for 7 days.

Table 1 Daily amount of dietary supplement suggested by the manifacturer

Daily ratio	
Weight (Kg)	Amount (g)
1 – 10	30 – 180
11 – 20	190 – 300
21 – 35	310 – 455
36 – 50	465 – 595

The diets

The two diets were based on the same receipt and completely fulfil the recommendations for proteins, carbohydrates and fats content in order to obtain a complete food for a daily ration in dog (as reported in Nutritional Guidelines for complete and complementary pet food for cats and dogs by The European Pet Food Industry Federation). In particular, the two foods reported similar analytical composition in nutrients (24 % of crude protein, 12 % of crude oils and fats, 3.7 %, of crude fibre 5 % of crude ash, 9 % of moisture) and, as a consequence, similar Metabolised Energy (ME) of 3.477 kcal/kg corresponding to 14.6 MJ/kg. Both foods are commercially available and in the form of kibbles industrially produced with extrusion technique. The specific nutraceutical diet was composed by two mixed components: kibbles, included in the ideal percentage of 93–94 % in weight, and cold-pressed microcapsules at the 6–7 % in weight of complete food (European patent n.EP 2526781). Overall nutrient profile of the product was obtained by the sum of a first nutrient profile of the kibbles, for feeding purpose, and a second nutrient profile of the microcapsules for both nutrient and therapeutic purposes. Microcapsules were composed of 60–80 % of hydrolyzed proteins (of fish and vegetable origin), 20–40 % of minerals, used as glidants, and therapeutical substances (*Melaleuca alternifolia*, 0.00343 %, *Tilia platyphyllos scapoli et cordata,* 0.0147 %, *Allium sativum L.,* 0.0245 %, *Rosa canina L.,* 0.098 %, and Zinc, 0.00479 %).

Malassezia pachydermatis determination

A small-tip cotton swab was inserted into the external ear canal removing some exudate. The swab was then rolled along a microscope slide with the sequence number. The slides were dried and stained with modified Wright's stain, and evaluated microscopically (Cole et al. 2007) with an Olympus 60BX polarized light microscope (New York Microscope Company Inc, Hicksville, NY, USA). *Malassezia pachydermatis* organisms were identified morphologically. The sample was considered pathological if the average of identified yeasts resulted more than 10 per high-

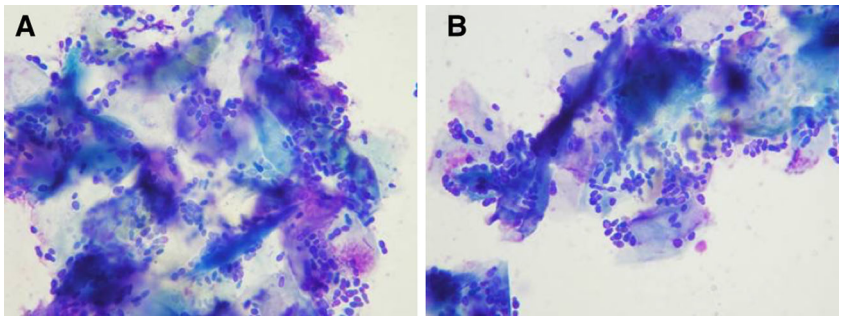

Fig. 1 Microscopic image of *Malassezia* presence. Microscope image (100X) highlighting the presence of several *Malassezia pachydermatis* organisms along with epithelial cells at different mature stages.

power field (HPF) in several fields, (Fig. 1) (Cowell et al. 2008). The precedure was performed before intervention (time 0); after 30 days (time 30); after 60 days (time 60) and at the end of intervention (time 90).

Clinical evaluation and scoring system

Dogs received veterinary inspections, before intervention (time 0); after 30 days (time 30); after 60 days (time 60) and at the end of intervention (time 90).

Operative procedures and animal care were performed in compliance with the national and international regulations (Italian regulation D.L.vo 116/1992 and European Union regulation 86/609/EC). The protocol was examined and approved prior to the beginning of the study by the Veterinary Ethical Review Committee. The recommendations of the ARRIVE guidelines in animal research were also consulted and considered (Kilkenny et al. 2012).

Immediately before treatment, and at the end, the condition of the ears was assessed always by the same operator and scored for the following clinical signs (Hawkins et al. 2010):

- Occlusion of ear canal (0–3); 0 = normal, 1 = occluded (but possible to insert a 6 mm otoscope (Operative Otoscope, HEINE Optotechnik, Herrsching, Germany) nozzle into the vertical ear canal), 2 = occluded (but possible to insert a 4 mm nozzle), 3 = occluded (not possible to insert a 4 mm nozzle).
- Erythema (0–3); 0 = normal, 1 = mild, 2 = moderate, 3 = severe.
- Discharge quantity (0–3); 0 = absent, 1 = slight, 2 = moderate, 3 = profuse.
- Odor (0–3); 0 = absent, 1 = mild, 2 = moderate, 3 = intense.

Statistical analysis

Data were analyzed using GraphPad Prism 6 software (GraphPad Software, Inc., La Jolla, CA, USA). All data are presented as the means ± standard error of the mean and were first checked for normality test using the D'Agostino-Pearson normality test. Differences in occlusion of the ear, erythema, discharge quantity and odor score between the two supplements at the end of treatment versus baseline for each ear were analyzed using a two-way analysis of variance (ANOVA) followed by Sidak's multiple comparisons test. A $p < 0.05$ was considered significant.

Results

Following clinical and cytological evaluation 28 out of 30 dogs presented an excessive amount of ear wax related to *Malassezia pachydermatis* infection. Only 2 out of 30 dogs reported an additional bacterial presence (either cocci or bacilli), therefore we considered such condition as not worth of clinical monitoring.

No adverse effects, such as cutaneous atrophy, secondary infections (Muller et al. 2001), increased licking (Bensignor and Olivry 2005), occasional skin itching or burning (Caffier

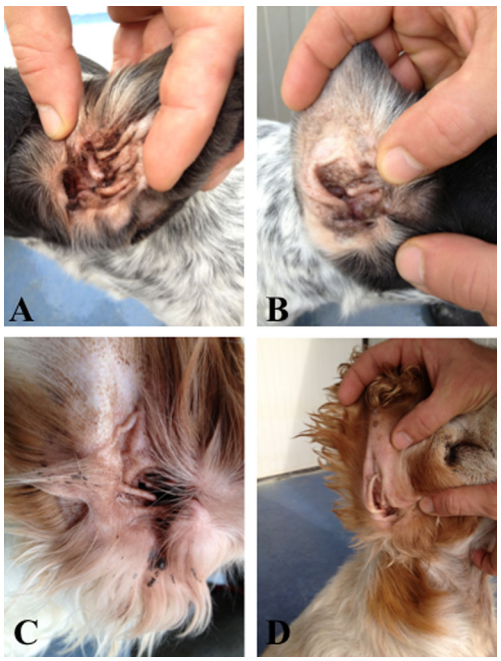

Fig. 2 Ears improvement after 90 days of evaluation with specific nutraceutical diet, (**a-c**) ears before the evaluation (time = 0), (**b-d**) ears at the end of the evaluation (time = 90)

et al. 2007) and hearing loss (Mason et al. 2013) were reported by the owners or noted on otoscopic examinations with any treatment, and all dogs completed the 90-day evaluation period. In Fig. 2, the overall improvement of dogs hears before and at the end of the 90-days evaluation is shown (Fig. 2).

The nutraceutical diet significantly decreased dog's ear canal occlusion, erythema, odor and mucus discharge scores after 90 days of evaluation, if compared with baseline while the mean number of *Malassezia pachydermatis* organisms slightly decresed (Fig. 3).

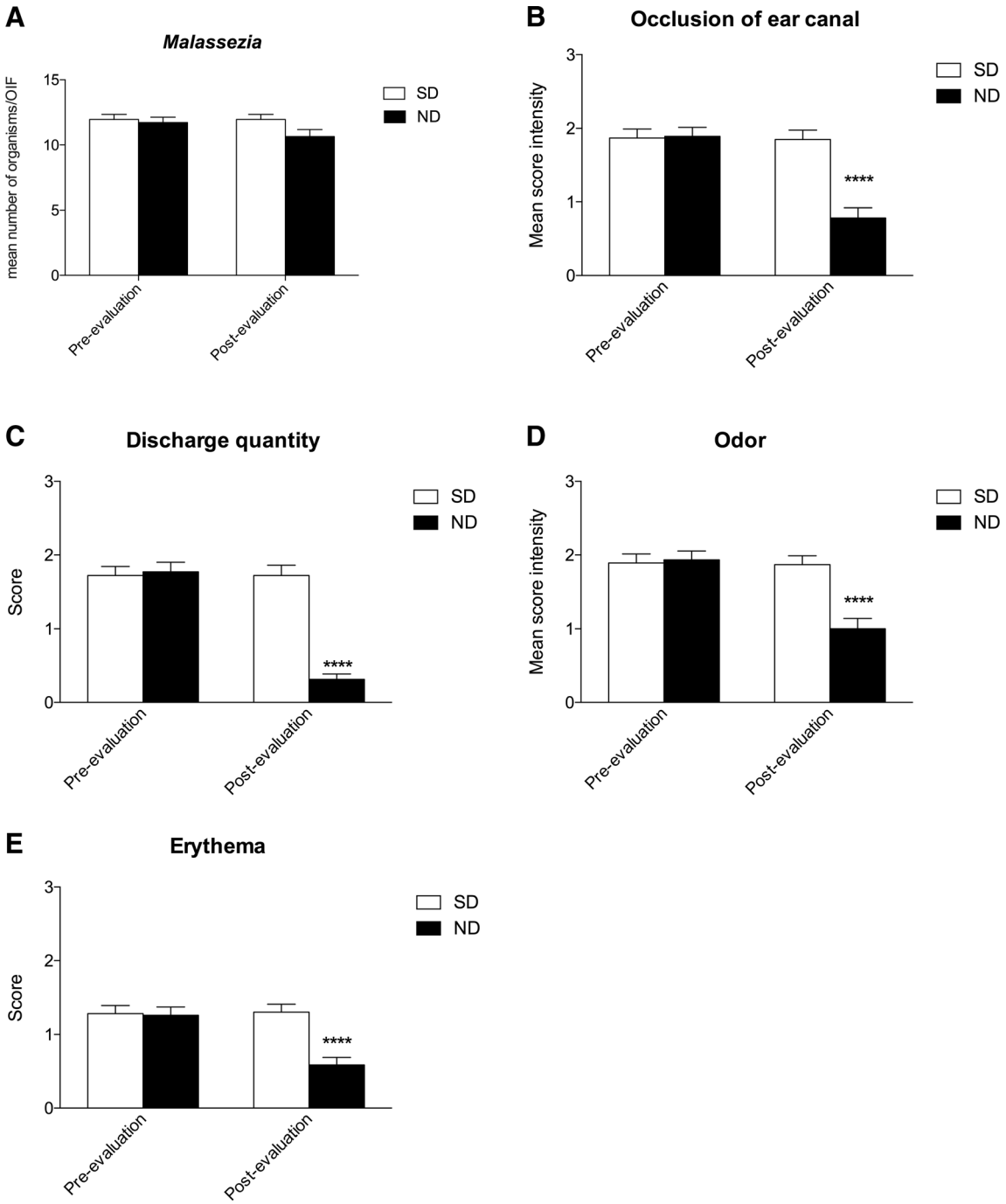

Fig. 3 Graphical representations of symptoms trend during the evaluation. (**a**) Mean *Malassezia* organisms in OIF before and after 90 days of evaluation for SD and ND group, organisms resulted slightly decreased in ND group; (**b**) mean occlusion of ear canal score before and after 90 days of evaluation for SD and ND group, a significant decrease (****$P < 0.0001$) was observed in ND group; (**c**) mean discharge quantity score before and after 90 days of evaluation for SD and ND group, a significant decrease (****$P < 0.0001$) was observed in ND group t; (**d**) mean odor score before and after 90 days of evaluation for SD and ND group, a significant decrease (****$P < 0.0001$) was observed in ND group; (**e**) mean erythema score before and after 90 days of evaluation for SD and ND group, a significant decrease (****$P < 0.0001$) was observed in ND group

After 90-days of evaluation *Malassezia pachydermatis* organisms decreased from a baseline value of 5.32 ± 0.4 to 4.2 ± 0.3 in the ND group and from a baseline value of 5.4 ± 0.4 to 5.4 ± 0.3 in the SD group (Fig. 3a).

Dogs ear canal occlusion resulted decresead from a baseline value of 1.87 ± 0.1 to 1.84 ± 0.1 in the SD group and from a baseline value of 1.89 ± 0.1 to 0.78 ± 0.1 in the ND group (Fig. 3b, ****$P < 0.0001$).

As to discharge quantity, the scores decreased from a baseline value of 1.72 ± 0.1 to 1.74 ± 0.1 in the SD group and from a baseline value of 1.77 ± 0.1 to 0.31 ± 0.07 in the ND group (Fig. 3c, ****$P < 0.0001$). Also odor scores resulted decreased after 90-days of evaluation, with respect to the baseline.

More in details, the scores decreased from a baseline value of 1.89 ± 0.1 to 1.87 ± 0.1 in the SD group and from a baseline value of 1.91 ± 0.1 to 1.0 ± 0.1 in the ND group (Fig. 3d, ****$P < 0.0001$).

Finally, erythema dicreased from a baseline value of 1.28 ± 0.1 to 1.30 in the SD group and from a baseline value of 1.26 ± 0.1 to 0.58 ± 0.1 in the ND group (Fig. 3e, ****$P < 0.0001$).

Discussion

Dogs affected by chronic, recurrent otitis externa are considered one of the most frustrating pathologies of daily veterinary clinical practice (Rosser 2004).

In this study, we use a specific nutraceutical diet, based on a combination of fish hydrolyzed proteins, rice carbohydrates, *Melaleuca alternifolia, Tilia cordata, Allium sativum L, Rosa canina L.,* Zinc and a Omega3/6 (1:0.8 ratio), as an adiuvant approach for the clinical management of canine otitis externa.

We observed a significant and encouraging reduction of the main symptoms of otitis externa - as the external ear canal occlusion, erythema, odor and mucus discharge - in enrolled dogs fed the nutraceutical diet if compared to those who received the standard diet. To this regard, we recently described the efficacy of a similar diet in relieving some otitis externa clinical symptoms, such as malodor, shaking, pus presence, earwax, itch, edema, blood presence, auricular function and auricular flush, in 107 dogs after 30 days of evaluation (Di Cerbo et al. 2014).

Our results appear in agreement with those observed by Sarrell et al. that compared the effectiveness of a naturopathic herbal extract, containing also *Allium sativum,* with anaesthetic ear drops in the management of ear pain associated with acute otitis media (Sarrell et al. 2001). Specifically, 61 out of 103 children treated with naturopathic herbal extract had an overall improvement in ear pain score due to analgesic, anti-inflammatory, anti-occlusive effects and anti-infective properties of the naturopathic product.

Here, we evidenced that the specific nutraceutical diet was also highly tolerated throughout the whole evaluation period as no adverse effects were observed in all dogs completing the study. In addition, we observed that most of clinical symptoms were substantially halved. These intersting occurences strongly encourage the use of the nutraceutical diets, endowed with anti-inflammatory and antioxidant acitivities, as valid and safe support to the conventional pharmacological therapy for dogs affected by chronic otits externa.

With regard to comorbidity of *Malassezia* infection, the addition of zinc in our diet was based on previous *in vitro* and *in vivo* studies, which highlighted its role in reducing yeasts number (DeAngelis et al. 2005; Mendelsohn et al. 2005). However, clinically apparent yeast presence seemed unvaried in the SD group. Althought our study showed a slightly reduction in the number of *Malassezia pachydermatis* organisms in ND group, it is reasonable to hypothesize a possible synergistic action of this antiinflammatory and antioxidant diet with antibiotic therapy. In this regard, therapy usually is topically applied for a reduced time, in order to avoid an antibiotic resistance phenomenon. It is noteworthy that an increased risk of antibiotic resistance may occur after a routine topical antibiotic administration in the treatment of otitis externa (Voget et al. 2012). In this respect, the anti-inflammatory and antioxidant effects of a diet could likely reduce the needing and the frequency of local antibiotic administration and contribute to avoid the emergence of drug resistence.

The results achieved in this study, concerning ear canal occlusion and erythema, are in agreement with those observed by Sarrell et al. that compared the effectiveness of a naturopathic herbal extract, containing also *Allium sativum,* with anaesthetic ear drops in the management of ear pain associated with acute otitis media (Sarrell et al. 2001). Specifically, the authors reported that 61 out of 103 children, belonging to the naturopathic herbal extract-treated group, had an overall improvement in ear pain score due to analgesic, antiinflammatory, anti-occlusive effects and anti-infective properties of the naturopathic product.

Many studies, regarding both dog and human, claim for nutraceutical administration benefits in otitis externa. Our investigation further outlines the quick symptoms relieving of otitis externa by means of a commercially available nutraceutical diet.

To the best of our knowledge this is the first report of a veterinary clinical evaluation concerning a anti-inflammatory and antioxidant diet effect on dogs affected by chronic otitis externa. Although further studies with a larger sample and time of observation are needed these results can be considered very promising in light of a possible traslation on the human side.

Acknowledgments This article was not supported by grants. The authors thank Dr. S. Saorin for the professional editing of the manuscript.

Compliance with ethical standards

Conflict of interest statement The authors declare that they have no conflict of interest. This research was performed in collaboration with some scientists from the Division of Research and Development, Sanypet SpA, Padova, Italy (as indicated in the Author's affiliation) according to scientific and ethical principles of the scientific community. No financial funding was obtained from Sanypet Industry for this research study.

References

Adetumbi M, Javor GT, Lau BH (1986) Allium sativum (garlic) inhibits lipid synthesis by Candida albicans. Antimicrob Agents Chemother 30:499–501

Agius AM, Pickles JM, Burch KL (1992) A prospective study of otitis externa. Clin otolaryngol Allied Sci 17:150–154

Allison GL, Lowe GM, Rahman K (2012) Aged garlic extract inhibits platelet activation by increasing intracellular cAMP and reducing the interaction of GPIIb/IIIa receptor with fibrinogen. Life Sci 91: 1275–1280. doi:10.1016/j.lfs.2012.09.019

Amagase H, Milner JA (1993) Impact of various sources of garlic and their constituents on 7,12-dimethylbenz[a]anthracene binding to mammary cell DNA. Carcinogenesis 14:1627–1631

An M, Shen H, Cao Y, Zhang J, Cai Y, Wang R, Jiang Y (2009) Allicin enhances the oxidative damage effect of amphotericin B against Candida albicans. Int J Antimicrob Agents 33:258–263. doi:10.1016/j.ijantimicag.2008.09.014

Ashraf R, Khan RA, Ashraf I, Qureshi AA (2013) Effects of Allium sativum (garlic) on systolic and diastolic blood pressure in patients with essential hypertension. Pak J Pharm Sci 26:859–863

Baldissera MD et al (2014) Effect of tea tree oil (Melaleuca alternifolia) on the longevity and immune response of rats infected by Trypanosoma evansi. Res Vet Sci 96:501–506. doi:10.1016/j.rvsc.2014.03.013

Banerjee SK, Maulik M, Manchanda SC, Dinda AK, Das TK, Maulik SK (2001) Garlic-induced alteration in rat liver and kidney morphology and associated changes in endogenous antioxidant status. Food Chem Toxicol: Int J Published Br Ind Biol Res Assoc 39:793–797

Banerjee SK, Dinda AK, Manchanda SC, Maulik SK (2002) Chronic garlic administration protects rat heart against oxidative stress induced by ischemic reperfusion injury. BMC Pharmacol 2:16

Beers SL, Abramo TJ (2004) Otitis externa review. Pediatr Emerg Care 20:250–256

Bensignor E, Olivry T (2005) Treatment of localized lesions of canine atopic dermatitis with tacrolimus ointment: a blinded randomized controlled trial. Vet Dermatol 16:52–60. doi:10.1111/j.1365-3164.2005.00419.x

Bonaventura P, Benedetti G, Albarede F, Miossec P (2014) Zinc and its role in immunity and inflammation. Autoimmun Rev. doi:10.1016/j.autrev.2014.11.008

Bordia A, Verma SK, Srivastava KC (1998) Effect of garlic (Allium sativum) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostaglandins Leukot Essent Fat Acids 58:257–263

Caffier PP, Harth W, Mayelzadeh B, Haupt H, Sedlmaier B (2007) Tacrolimus: a new option in therapy-resistant chronic external otitis. Laryngoscope 117:1046–1052. doi:10.1097/MLG.0b013e31804b1aad

Caldefie-Chezet F, Fusillier C, Jarde T, Laroye H, Damez M, Vasson MP, Guillot J (2006) Potential anti-inflammatory effects of Melaleuca alternifolia essential oil on human peripheral blood leukocytes. Phytother Res: PTR 20:364–370. doi:10.1002/ptr.1862

Capasso A (2013) Antioxidant action and therapeutic efficacy of Allium sativum L. Molecules 18:690–700. doi:10.3390/molecules18010690

Carson CF, Hammer KA, Riley TV (2006) Melaleuca alternifolia (Tea tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbiol Rev 19:50–62. doi:10.1128/CMR.19.1.50-62.2006

Chaupis-Meza D, Rojas J, Gasco M, Gonzales GF (2014) [Hypotensive effect of extract of macerated garlic (Allium sativum) for 18 weeks in an in vivo experimental model]. Rev Peru Med Exp Salud Publica 31:461–466

Chrubasik C, Roufogalis BD, Muller-Ladner U, Chrubasik S (2008) A systematic review on the Rosa canina effect and efficacy profiles. Phytother Res: PTR 22:725–733. doi:10.1002/ptr.2400

Cole LK, Luu DH, Rajala-Schultz PJ, Meadows C, Torres AH (2007) In vitro activity of an ear rinse containing tromethamine, EDTA, benzyl alcohol and 0.1% ketoconazole on Malassezia organisms from dogs with otitis externa. Vet Dermatol 18:115–119. doi:10.1111/j.1365-3164.2007.00583.x

Colombini S (1999) Canine zinc-responsive dermatosis the veterinary clinics of North America. Small Anim Pract 29:1373–1383

Cowell RL, Tyler RD, Meinkoth JH, DeNicola DB (2008) Diagnostic Cytology and Hematology of the Dog and Cat, 3rd edn. Mosby, Elsevier, Canada

Crespo MJ, Abarca ML, Cabanes FJ (2002) Occurrence of Malassezia spp. in the external ear canals of dogs and cats with and without otitis externa. Med Mycol 40:115–121

Dalwai S, Rodrigues SJ, Baliga S, Shenoy VK, Shetty TB, Pai UY, Saldanha S (2014) Comparative evaluation of antifungal action of tea tree oil, chlorhexidine gluconate and fluconazole on heat polymerized acrylic denture base resin - an in vitro study. Gerodontology. doi:10.1111/ger.12176

Daneshrad D, Kim JC, Amedee RG (2002) Acute otitis externa. J La State Med Soc: Off Organ J La State Med Soc 154:226–228

Davitashvili DT, Museridze DP, Svanidze IK, Pavliashvili NS, Sanikidze TV (2010) [Correction of oxidative stress in the rat brain cortical cellular culture with vitamines E and C] Georgian Med News 56–60

de Campos Rasteiro VM et al (2014) Essential oil of Melaleuca alternifolia for the treatment of oral candidiasis induced in an immunosuppressed mouse model. BMC Complement Alternat Med 14: 489. doi:10.1186/1472-6882-14-489

DeAngelis YM, Gemmer CM, Kaczvinsky JR, Kenneally DC, Schwartz JR, Dawson TL Jr (2005) Three etiologic facets of dandruff and seborrheic dermatitis: malassezia fungi, sebaceous lipids, and individual sensitivity. J Investig Dermatol Symp Proc 10:295–297. doi:10.1111/j.1087-0024.2005.10119.x

Deliorman Orhan D, Hartevioglu A, Kupeli E, Yesilada E (2007) In vivo anti-inflammatory and antinociceptive activity of the crude extract and fractions from Rosa canina L. fruits. J Ethnopharmacol 112: 394–400. doi:10.1016/j.jep.2007.03.029

DeLuca P, Rossetti RG, Alavian C, Karim P, Zurier RB (1999) Effects of gammalinolenic acid on interleukin-1 beta and tumor necrosis factor-alpha secretion by stimulated human peripheral blood monocytes: studies in vitro and in vivo. J Investig Med: Off Publ Am Fed Clin Res 47:246–250

Di Cerbo A, Palmieri B, Chiavolelli F, Guidetti G, Sergio C (2014) Functional foods in pets and humans intern. J Appl Res Vet Med 12:192–199

Dini C, Fabbri A, Geraci A (2011) The potential role of garlic (Allium sativum) against the multi-drug resistant tuberculosis pandemic: a

review. Ann Ist Super Sanita 47:465–473. doi:10.4415/ANN_11_04_18
Engelen MA, Anthonissens E (2000) Efficacy of non-acaricidal containing otic preparations in the treatment of otoacariasis in dogs and cats. Vet Rec 147:567–569
Engelen M, De Bock M, Hare J, Goossens L (2010) Effectiveness of an otic product containing miconazole, polymyxin B and prednisolone in the treatment of canine otitis externa: multi-site field trial in the US and Canada. Int J Appl Res Vet Med 8:21
Fanelli SL, Castro GD, de Toranzo EG, Castro JA (1998) Mechanisms of the preventive properties of some garlic components in the carbon tetrachloride-promoted oxidative stress. Diallyl sulfide; diallyl disulfide; allyl mercaptan and allyl methyl sulfide. Res Commun Mol Pathol Pharmacol 102:163–174
Furneri PM, Paolino D, Saija A, Marino A, Bisignano G (2006) In vitro antimycoplasmal activity of Melaleuca alternifolia essential oil. J Antimicrob Chemother 58:706–707. doi:10.1093/jac/dkl269
Ghannoum MA (1988) Studies on the anticandidal mode of action of Allium sativum (garlic). J Gen Microbiol 134:2917–2924
Greay SJ, Ireland DJ, Kissick HT, Heenan PJ, Carson CF, Riley TV, Beilharz MW (2010) Inhibition of established subcutaneous murine tumour growth with topical Melaleuca alternifolia (tea tree) oil. Cancer Chemother Pharmacol 66:1095–1102. doi:10.1007/s00280-010-1267-3
Guo NL, Lu DP, Woods GL, Reed E, Zhou GZ, Zhang LB, Waldman RH (1993) Demonstration of the anti-viral activity of garlic extract against human cytomegalovirus in vitro. Chin Med J 106:93–96
Gurbuz I, Ustun O, Yesilada E, Sezik E, Kutsal O (2003) Anti-ulcerogenic activity of some plants used as folk remedy in Turkey. J Ethnopharmacol 88:93–97
Halpern MT, Palmer CS, Seidlin M (1999) Treatment patterns for otitis externa. J Am Board Fam Pract / Am Board Fam Pract 12:1–7
Hammer KA (2015) Treatment of acne with tea tree oil (melaleuca) products: a review of efficacy, tolerability and potential modes of action. Int J Antimicrob Agents 45:106–110. doi:10.1016/j.ijantimicag.2014.10.011
Hannley MT, Denneny JC 3rd, Holzer SS (2000) Use of ototopical antibiotics in treating 3 common ear diseases. Otolaryngol Head Neck Surg: Off J Am Acad Otolaryngol Head Neck Surg 122:934–940
Hawkins C, Harper D, Burch D, Anggard E, Soothill J (2010) Topical treatment of Pseudomonas aeruginosa otitis of dogs with a bacteriophage mixture: a before/after clinical trial. Vet Microbiol 146:309–313. doi:10.1016/j.vetmic.2010.05.014
Hensel P (2010) Nutrition and skin diseases in veterinary medicine. Clin Dermatol 28:686–693. doi:10.1016/j.clindermatol.2010.03.031
Ireland DJ, Greay SJ, Hooper CM, Kissick HT, Filion P, Riley TV, Beilharz MW (2012) Topically applied Melaleuca alternifolia (tea tree) oil causes direct anti-cancer cytotoxicity in subcutaneous tumour bearing mice. J Dermatol Sci 67:120–129. doi:10.1016/j.jdermsci.2012.05.005
Jager AK, Eldeen IM, van Staden J (2007) COX-1 and −2 activity of rose hip. Phytother Res: PTR 21:1251–1252. doi:10.1002/ptr.2236
Jager AK, Petersen KN, Thomasen G, Christensen SB (2008) Isolation of linoleic and alpha-linolenic acids as COX-1 and −2 inhibitors in rose hip. Phytother Res: PTR 22:982–984. doi:10.1002/ptr.2446
Johansson ML et al (1998) Survival of Lactobacillus plantarum DSM 9843 (299v), and effect on the short-chain fatty acid content of faeces after ingestion of a rose-hip drink with fermented oats. Int J Food Microbiol 42:29–38
Jonkers D, Sluimer J, Stobberingh E (1999) Effect of garlic on vancomycin-resistant enterococci. Antimicrob Agents Chemother 43:3045
Karuppiah P, Rajaram S (2012) Antibacterial effect of Allium sativum cloves and Zingiber officinale rhizomes against multiple-drug resistant clinical pathogens. Asian Pac J Trop Biomed 2:597–601. doi:10.1016/S2221-1691(12)60104-X
Kelley DS et al (1999) Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men. Lipids 34:317–324
Khalil Z, Pearce AL, Satkunanathan N, Storer E, Finlay-Jones JJ, Hart PH (2004) Regulation of wheal and flare by tea tree oil: complementary human and rodent studies. J invest Dermatol 123:683–690. doi:10.1111/j.0022-202X.2004.23407.x
Kilkenny C, Browne WJ, Cuthi I, Emerson M, Altman DG (2012) Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. Veter Clin Pathol / Am Soc Vet Clin Pathol 41:27–31. doi:10.1111/j.1939-165X.2012.00418.x
Koh KJ, Pearce AL, Marshman G, Finlay-Jones JJ, Hart PH (2002) Tea tree oil reduces histamine-induced skin inflammation. Br J Dermatol 147:1212–1217
Larsen E, Kharazmi A, Christensen LP, Christensen SB (2003) An antiinflammatory galactolipid from rose hip (Rosa canina) that inhibits chemotaxis of human peripheral blood neutrophils in vitro. J Nat Prod 66:994–995. doi:10.1021/np0300636
Lattanzio F, Greco E, Carretta D, Cervellati R, Govoni P, Speroni E (2011) In vivo anti-inflammatory effect of Rosa canina L. extract. J Ethnopharmacol 137:880–885. doi:10.1016/j.jep.2011.07.006
Lau BH (2001) Suppression of LDL oxidation by garlic. J Nutr 131:985S–988S
Lin MC, Wang EJ, Patten C, Lee MJ, Xiao F, Reuhl KR, Yang CS (1996) Protective effect of diallyl sulfone against acetaminophen-induced hepatotoxicity in mice. J Biochem Toxicol 11:11–20. doi:10.1002/(SICI)1522-7146(1996)11:1<11::AID-JBT2>3.0.CO;2-Y
Lin JG, Chen GW, Su CC, Hung CF, Yang CC, Lee JH, Chung JG (2002) Effects of garlic components diallyl sulfide and diallyl disulfide on arylamine N-acetyltransferase activity and 2-aminofluorene-DNA adducts in human promyelocytic leukemia cells. Am J Chin Med 30:315–325. doi:10.1142/S0192415X02000338
Logas DB (1994) Diseases of the ear canal the veterinary clinics of North America. Small Anim Pract 24:905–919
Majewski M (2014) Allium sativum: facts and myths regarding human health. Rocz Panstw Zakl Hig 65:1–8
Mantil E, Daly G, Avis TJ (2015) Effect of tea tree (Melaleuca alternifolia) oil as a natural antimicrobial agent in lipophilic formulations. Can J Microbiol 61:82–88. doi:10.1139/cjm-2014-0667
Maslin DJ, Brown CA, Das I, Zhang XH (1997) Nitric oxide–a mediator of the effects of garlic? Biochem Soc Trans 25:408S
Mason CL, Paterson S, Cripps PJ (2013) Use of a hearing loss grading system and an owner-based hearing questionnaire to assess hearing loss in pet dogs with chronic otitis externa or otitis media. Vet Dermatol 24:512–e121. doi:10.1111/vde.12057
McKeever PJ, Torres SM (1997) Ear disease and its management the veterinary clinics of North America. Small Anim Pract 27:1523–1536
Mendelsohn CL, Griffin CE, Rosenkrantz WS, Brown LD, Boord MJ (2005) Efficacy of boric-complexed zinc and acetic-complexed zinc otic preparations for canine yeast otitis externa. J Am Anim Hosp Assoc 41:12–21. doi:10.5326/0410012
Mikus J, Harkenthal M, Steverding D, Reichling J (2000) In vitro effect of essential oils and isolated mono- and sesquiterpenes on Leishmania major and Trypanosoma brucei. Planta Med 66:366–368. doi:10.1055/s-2000-8548
Muller GH, Scott DW, Kirk RW, Miller WH, Griffin CE (2001) Muller & Kirk's Small Animal Dermatology. Saunders
Ninomiya K, Matsuda H, Kubo M, Morikawa T, Nishida N, Yoshikawa M (2007) Potent anti-obese principle from Rosa canina: structural requirements and mode of action of trans-tiliroside. Bioorg Med Chem Lett 17:3059–3064. doi:10.1016/j.bmcl.2007.03.051
Nogueira MN, Aquino SG, Rossa Junior C, Spolidorio DM (2014) Terpinen-4-ol and alpha-terpineol (tea tree oil components) inhibit the production of IL-1beta, IL-6 and IL-10 on human macrophages.

Inflamm Res: Off J Eur Histamine Res Soc [et al] 63:769–778. doi:10.1007/s00011-014-0749-x

Osguthorpe JD, Nielsen DR (2006) Otitis externa: review and clinical update. Am Fam Physician 74:1510–1516

Peano A, Beccati M, Chiavassa E, Pasquetti M (2012) Evaluation of the antifungal susceptibility of Malassezia pachydermatis to clotrimazole, miconazole and thiabendazole using a modified CLSI M27-A3 microdilution method. Vet Dermatol 23(131–135):e129. doi:10.1111/j.1365-3164.2011.01025.x

Pearce AL, Finlay-Jones JJ, Hart PH (2005) Reduction of nickel-induced contact hypersensitivity reactions by topical tea tree oil in humans. Inflamm Res: Off J Eur Histamine Res Soc [et al] 54:22–30. doi:10.1007/s00011-004-1317-6

Perez HA, De la Rosa M, Apitz R (1994) In vivo activity of ajoene against rodent malaria. Antimicrob Agents Chemother 38:337–339

Pietschmann S, Meyer M, Voget M, Cieslicki M (2013) The joint in vitro action of polymyxin B and miconazole against pathogens associated with canine otitis externa from three European countries. Vet Dermatol 24:439–445. doi:10.1111/vde.12037, **e496-437**

Porter RS (2011) The Merck Manual of Diagnosis and Therapy. Wiley

Prasad K, Laxdal VA, Yu M, Raney BL (1996) Evaluation of hydroxyl radical-scavenging property of garlic. Mol Cell Biochem 154:55–63

Rashid A, Khan HH (1985) The mechanism of hypotensive effect of garlic extract JPMA. J Pak Med Assoc 35:357–362

Reinhart KM, Coleman CI, Teevan C, Vachhani P, White CM (2008) Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. Ann Pharmacother 42:1766–1771. doi:10.1345/aph.1L319

Ried K, Frank OR, Stocks NP (2010) Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. Maturitas 67:144–150. doi:10.1016/j.maturitas.2010.06.001

Rosser EJ Jr (2004) Causes of otitis externa the veterinary clinics of North America. Small Anim Pract 34:459–468. doi:10.1016/j.cvsm.2003.10.006

Rosychuk RA (1994) Management of otitis externa the veterinary clinics of North America. Small Anim Pract 24:921–952

Roth L (1988) Pathologic changes in otitis externa the veterinary clinics of North America. Small Anim Pract 18:755–764

Rougier S, Borell D, Pheulpin S, Woehrle F, Boisrame B (2005) A comparative study of two antimicrobial/anti-inflammatory formulations in the treatment of canine otitis externa. Vet Dermatol 16:299–307. doi:10.1111/j.1365-3164.2005.00465.x

Russo A et al (2000) Bioflavonoids as antiradicals, antioxidants and DNA cleavage protectors. Cell Biol Toxicol 16:91–98

Sadigh-Eteghad S, Tayefi-Nasrabadi H, Aghdam Z, Zarredar H, Shanehbandi D, Khayyat L, Seyyed-Piran SH (2011) Rosa canina L. fruit hydro-alcoholic extract effects on some immunological and biochemical parameters in rats. Bioimpacts : BI 1:219–224. doi:10.5681/bi.2011.031

Sander R (2001) Otitis externa: a practical guide to treatment and prevention. Am Fam Physician 63:927–936, **941–922**

Sarrell EM, Mandelberg A, Cohen HA (2001) Efficacy of naturopathic extracts in the management of ear pain associated with acute otitis media. Arch Pediatr Adolesc Med 155:796–799

Scherl M, Muller T, Krautler B (2012) Chlorophyll catabolites in senescent leaves of the lime tree (Tilia cordata). Chem Biodivers 9:2605–2617. doi:10.1002/cbdv.201200203

Shams-Ghahfarokhi M et al (2006) In vitro antifungal activities of Allium cepa, Allium sativum and ketoconazole against some pathogenic yeasts and dermatophytes. Fitoterapia 77:321–323. doi:10.1016/j.fitote.2006.03.014

Shiota S, Shimizu M, Mizusima T, Ito H, Hatano T, Yoshida T, Tsuchiya T (2000) Restoration of effectiveness of beta-lactams on methicillin-resistant Staphylococcus aureus by tellimagrandin I from rose red. FEMS Microbiol Lett 185:135–138

Sies H, Stahl W, Sundquist AR (1992) Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. Ann N Y Acad Sci 669:7–20

Sobenin IA, Andrianova IV, Fomchenkov IV, Gorchakova TV, Orekhov AN (2009) Time-released garlic powder tablets lower systolic and diastolic blood pressure in men with mild and moderate arterial hypertension. Hypertens Res: Off J Jpn Soc Hypertens 32:433–437. doi:10.1038/hr.2009.36

Sood S, Strachan DR, Tsikoudas A, Stables GI (2002) Allergic otitis externa. Clin otolaryngol Allied Sci 27:233–236

Stabler SN, Tejani AM, Huynh F, Fowkes C (2012) Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients. Cochrane database of Syst Rev 8:CD007653. doi:10.1002/14651858.CD007653.pub2

Studdert VP, Hughes KL (1991) A clinical trial of a topical preparation of miconazole, polymyxin and prednisolone in the treatment of otitis externa in dogs. Aust Vet J 68:193–195

Sumiyoshi H, Wargovich MJ (1990) Chemoprevention of 1,2-dimethylhydrazine-induced colon cancer in mice by naturally occurring organosulfur compounds. Cancer Res 50:5084–5087

Szymona M (1952) [Effect of phytoncides of Allium sativum on growth and respiration of certain pathogenic fungi]. Acta Microbiol Pol 1:5–23

Tadi PP, Lau BH, Teel RW, Herrmann CE (1991a) Binding of aflatoxin B1 to DNA inhibited by ajoene and diallyl sulfide. Anticancer Res 11:2037–2041

Tadi PP, Teel RW, Lau BH (1991b) Organosulfur compounds of garlic modulate mutagenesis, metabolism, and DNA binding of aflatoxin B1. Nutr Cancer 15:87–95. doi:10.1080/01635589109514116

Takashima M, Shichiri M, Hagihara Y, Yoshida Y, Niki E (2012) Capacity of peroxyl radical scavenging and inhibition of lipid peroxidation by beta-carotene, lycopene, and commercial tomato juice. Food Funct 3:1153–1160. doi:10.1039/c2fo30119a

Toker G, Aslan M, Yesilada E, Memisoglu M, Ito S (2001) Comparative evaluation of the flavonoid content in officinal Tiliae flos and Turkish lime species for quality assessment. J Pharm Biomed Anal 26:111–121

Trovato A, Monforte MT, Rossitto A, Forestieri AM (1996) In vitro cytotoxic effect of some medicinal plants containing flavonoids. Boll Chim Farm 135:263–266

Tsai Y, Cole LL, Davis LE, Lockwood SJ, Simmons V, Wild GC (1985) Antiviral properties of garlic: in vitro effects on influenza B, herpes simplex and coxsackie viruses. Planta Med 51:460–461. doi:10.1055/s-2007-969553

Tsikoudas A, Jasser P, England RJ (2002) Are topical antibiotics necessary in the management of otitis externa? Clin otolaryngol Allied Sci 27:260–262

Tsubura A, Lai YC, Kuwata M, Uehara N, Yoshizawa K (2011) Anticancer effects of garlic and garlic-derived compounds for breast cancer control. Anti Cancer Agents Med Chem 11:249–253

Tumbas VT, Canadanovic-Brunet JM, Cetojevic-Simin DD, Cetkovic GS, Ethilas SM, Gille L (2012) Effect of rosehip (Rosa canina L.) phytochemicals on stable free radicals and human cancer cells. J Sci Food Agric 92:1273–1281. doi:10.1002/jsfa.4695

Voget M, Armbruster M, Meyer M (2012) Antibiotic plasma levels in dogs with otitis externa treated routinely with various topical preparations. Berl Munch Tierarztl Wochenschr 125:441–448

Wallace GC et al (2013) Multi-targeted DATS prevents tumor progression and promotes apoptosis in ectopic glioblastoma xenografts in SCID mice via HDAC inhibition. J Neuro-Oncol 114:43–50. doi:10.1007/s11060-013-1165-8

Wallengren J (2011) Tea tree oil attenuates experimental contact dermatitis. Arch Dermatol Res 303:333–338. doi:10.1007/s00403-010-1083-y

Wang HC, Pao J, Lin SY, Sheen LY (2012) Molecular mechanisms of garlic-derived allyl sulfides in the inhibition of skin cancer

progression. Ann N Y Acad Sci 1271:44–52. doi:10.1111/j.1749-6632.2012.06743.x

Watson SP (1996) Book review. Platelets 7:367–370. doi:10.3109/09537109609023598

Weber ND, Andersen DO, North JA, Murray BK, Lawson LD, Hughes BG (1992) In vitro virucidal effects of Allium sativum (garlic) extract and compounds. Planta Med 58:417–423. doi:10.1055/s-2006-961504

Wenzig EM, Widowitz U, Kunert O, Chrubasik S, Bucar F, Knauder E, Bauer R (2008) Phytochemical composition and in vitro pharmacological activity of two rose hip (Rosa canina L.) preparations. Phytomed: Int J Phytother Phytopharmacol 15:826–835. doi:10.1016/j.phymed.2008.06.012

Wills ED (1956) Enzyme inhibition by allicin, the active principle of garlic. Biochem J 63:514–520