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The efficacy of neutraceuticals to alleviate dog osteoarthritis symptoms, a meta-analysis of case-control trials

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ABSTRACT

Osteoarthritis is a common condition in dogs. Non-steroidal anti-inflammatory drugs are currently the most widely used treatment option; however, their chronic use is associated with numerous malefic side effects, including death. There has been increased interest in alternative treatments and nutraceuticals have assumed fundamental importance. A number of individual studies and systematic reviews have been done, but no meta-analysis has been produced to date. By conducting a meta-analysis, we aimed to fill this research gap. We combined the results of 13 case placebo controlled trials in a single major study, to determine the efficacy of nutraceuticals in alleviating symptoms of osteoarthritis. A population of 638 dogs was used, from which 327 were treated with nutraceuticals and 321 were used as controls. A successful random effects model was adjusted ($P<0.001$), with a risk ratio of 0.62 within a 95% CI of [0.47; 0.81], favouring the use of nutraceuticals. The nutraceuticals used in the trials were green-lipped mussel, chondroitin sulphate, an extract of India and Java turmeric (P54FP), a homeopathic combination preparation known as Zeel®, Ω-3 fatty acids, deep sea fish oil, a mix of glucosamine with chondroitin sulphate and hyaluronic acid, and cannabidiol.

Key words: case-control trials; dog osteoarthritis; meta-analysis; nutraceuticals; pain relief

Introduction

Arthritis is a chronic condition commonly seen in large breed, obese and older dogs (D'ALTILIO et al., 2007) as well as in dogs suffering from a genetic predisposition, such as Labrador Retrievers and German Shepherds (ANDERSON et al., 2018). There are several types of arthritis: septic, immune-mediated and osteoarthritis (KAHN, 2010). Osteoarthritis (OA) is the most common form of canine arthritis (GUPTA et al., 2011), and according to JOHNSON et al. (2020) it affects around 20% of dogs over one year of age and 90% over five. Osteoarthrosis may affect any diarthrodial joint in the body including the hips, elbows, stifles, vertebral facet joints and metacarpophalangeal joints (FRANKLIN et al., 2009) and it affects all tissues within the joint (HENROTIN et al., 2005).

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Osteoarthrosis occurs as a result of morphological, biochemical, molecular and biochemical changes of cells and matrices, resulting in the softening and loss of articular cartilage, degeneration of subchondral bones, and the formation of osteophytes at bone margins (BUDSBERG and BARTGES, 2006). A reduction in the rate of cartilage synthesis and an imbalance between proteolytic enzymes and their inhibitors, regulated by proinflammatory cytokines, is the main cause (MOREAU et al., 2003). Chronic inflammation of the synovial membrane is also often present (FRITSCH et al., 2010). Dogs with clinically present OA show stiffness of joints, lameness and pain while moving (TEIXEIRA et al., 2016).

Clinical signs associated with canine OA include joint pain, limited movement, crepitus, and inflammation (BUDSBERG and BARTGES, 2006). Dogs presenting with OA are reluctant to perform normal daily activities such as walking and climbing stairs (MOREAU et al., 2007). As a result, OA often reduces the quality of life of the affected animal (IMHOFF et al., 2011).

Canine OA can be assessed qualitatively by radiographic and clinical examinations, and quantitatively most commonly using ground reaction forces (GRFs) on affected limbs (MOREAU et al., 2007). Kinematic gait analysis can also be used to evaluate objectively changes in joint angles, velocity, and the acceleration of changes in joint angles, but it tends to be used less frequently as it is more specialised and time consuming (FOX, 2007). Radiography is a useful tool when assessing canine osteoarthritis as it allows the visualisation of the disease pathology by non-invasive means (BUCKLAND-WRIGHT, 1994). However, radiography can only detect advanced OA rather than early cartilage degeneration (POLLARD et al., 2006). Clinical examinations objectively evaluate pain and abnormalities associated with canine OA, but are subject to discrepancies due to differing opinions on the level of pain an animal is suffering (FOX, 2007). There are a number of pain scoring systems available, however as there are variations, including the use of different outcome measuring units, the results are not standardized.

The condition cannot be cured and therefore treatment aims at managing the disease by preventing and slowing the progression and controlling the clinical signs associated with it (FRITSCH et al., 2010; ROUSH et al., 2010). Specifically, the primary aim of OA treatment is to the keep the dog mobile by managing pain associated with the disease (RYCHEL, 2010). This can be achieved through preventing inflammatory reactions and the breakdown of cartilage (BEYNEN and LEGERSTEE, 2010). Secondary aims of OA treatment include protecting the affected joint, providing nutritional support to the animal, and strengthening the joint (RYCHEL, 2010).

There are a wide range of management options available for canine OA, including surgery, pharmaceuticals, nutraceuticals, weight management and exercise, with the selected treatment option depending on both the affected joint and the patient (BOUND et al., 2011).

The techniques used in controlling OA can be categorised into two broad groups: management factors and pharmaceutical techniques. Management factors include correct nutrition, weight management, exercise, and physical therapy, whereas pharmaceutical techniques include the use of anti-inflammatory and analgesic medications such as non-steroidal anti-inflammatory drugs (NSAIDs) (FRITSCH et al., 2010). Currently, NSAIDs are the most widely used treatment option for canine OA as the evidence supporting their use is strong. However, chronic use of NSAIDS is associated with numerous side effects, including gastrointestinal bleeding and ulceration, renal failure, hepatic failure and death. There is also some evidence to suggest that long-term use of NSAIDS may accelerate cartilage degeneration (INNES et al., 2010). As a result, there has been increased interest in alternative treatments for canine OA (HIELM-BJÖRKMAN et al., 2009a).

Nutraceuticals are an alternative treatment option used in the treatment of human arthritis and as a result they have gained popularity in veterinary medicine (BUDSBERG and BARTGES, 2006). Nutraceuticals are food products with medical or health benefits, including the prevention and treatment of disease (VANDERWEERD et al.,

2012). It is believed that some nutraceuticals provide the body with several nutrients, essential for cartilage repair and reduction of inflammation (BIERER and BUI, 2002). So far there has been no evidence to suggest that nutraceuticals are associated with adverse effects (PUCHEU and DUHAUTOIS, 2009). However, there is conflicting evidence regarding the efficacy of these products.

Nutraceuticals are promoted as safe and effective treatments for canine OA (BEYNEN and LEGERSTEE, 2010). However, there are no legal requirements in Europe for the efficacy of nutraceuticals to be tested in order to market them. (VANDERWEERD et al., 2012). A systematic review conducted by VANDERWEERD et al. (2012) assessed the efficacy of nutraceuticals in alleviating clinical signs of osteoarthritis in several species. They found good evidence to suggest that canine diets supplemented with high quality omega-3 fatty acids or GLM significantly improved clinical signs of canine OA. Studies conducted by ROUSCH et al. (2010) and FRITSCH et al. (2010) also found that fish oil diet supplementation (including omega-3 fatty acids) resulted in the improvement of clinical signs of canine OA. A number of studies conducted by BIERER and BUI (2002) found evidence to suggest GLM powder is effective in reducing clinical signs associated with canine OA. However, there are also several studies that question the efficacy of nutraceuticals in alleviating clinical signs associated with canine osteoarthritis. A study conducted by DOBENECKER et al. (2002) found that clinical signs of OA in dogs did not significantly improve when the dogs were treated with GLM extract.

There have already been many studies conducted to assess the safety and efficacy of various nutraceuticals in treating canine OA, originating from systematic reviews (HEROITIN et al., 2005; ARAGON, et al., 2007; SANDERSON et al., 2009; VANDERWEERD, 2012). It would therefore be useful to combine the results of these studies to determine the efficacy of these products over a greater study population. By conducting this meta-analysis, we aim to contribute to this process.

Materials and methods

Identification of clinical trials. Trials were identified using the search engine b-on Biblioteca do Conhecimento Online (b-on.pt). The following key word and booleans were used: (Nutraceuticals or dietary supplements or fish oils) and (osteoarthritis or joint disease or arthritis) and (dogs). In total 12,783 hits were retrieved. Then we selected academic peer reviewed journals only and refined the list to 6482 hits. Then we selected relevant data bases only (Complementary Index, Academic Search Complete, Gale In Context-Science, Medline, Science Citation Index, Scopus, Directory of Open Access Journals, Science Direct, Supplemental Index, Scielo) and arrived at 6357 hits. Then we searched for articles from the last 20 years (2001 to 2021) and retrieved 5857 hits. Finally, we had 1066 hits by selecting the following topics: osteoarthritis, therapeutics, nutrition, dietary supplements, diet, dogs, dog, pharmacology, clinical trials, medicinal plants, pain. At this point we searched manually for relevant systematic reviews and clinical trials. We also used the systematic reviews to search for any possible relevant trials in their references.

Inclusion and exclusion criteria. We used only peer reviewed journal articles, selected according to the rules of the previous section. Moreover, we only included trials with a treatment group compared against a control group, where the control group was given a placebo. Also, the trials selected were based on dogs with clinical signs of osteoarthritis in any synovial joint.

Trials including a positive control group only, such as receiving NSAID, were excluded. However, we found two trials (HIELM-BJÖRKMAN et al., 2009a and HIELM-BJÖRKMAN 2009b) with a treatment group (nutraceutical), a positive control group (NSAID) and a negative control group (placebo). These two trials were included in this meta-analysis (data from the treatment and the negative control groups only).

We also included as one, three trials reported in the same article (the trials reported by BIERER and BUI, 2002) using exactly the same approach. We merged the data from these three trials since they differed only in the presentation of the

nutraceutical, using different versions of green-lipped mussel (GLM) (as a powder, incorporated into a treat or incorporated into a main meal) with same dosage.

We split the trial reported by DOBENECKER et al. (2002) in two. These authors used three groups of dogs, two fed with different nutraceuticals and a third control group. The same control dogs were used for both groups of treated dogs and therefore 19 dogs were entered twice as controls.

Several different outcome measures are used to evaluate the degree of OA in dogs: the pain score (visual analogue or Likert scale grading); locomotion score (visual analogue or Likert scale grading); the quality-of-life index (a mixture of scores including pain and lameness); vertically orientated ground reaction force, measured in a platform; and serum analysis normally used to complement one or more of the previous scores. Most trials in fact use a mixture of the above.

It is, therefore, difficult to find an outcome measure common to all the trials, allowing comparisons in a meta-analysis. We only selected trials reporting information allowing us to build a 2 x 2 table with positive and negative outcomes for both the treatment and control. With this strategy we were able to identify 13 trials with common grounds enabling comparisons.

The meta-analysis was performed using these 13 trials, identified in Table 1. Data collected ranged from 2001 to 2021. There were 648 dogs in these investigations, with 327 subjected to treatment with nutraceuticals, and 321 dogs used as controls. As explained before, 19 dogs used as controls were counted twice.

Statistics. The logarithm of the risk ratio (RR) was the outcome variable considered. The homogeneity of the data and the moderators were tested using Cochran's Q-test. The percentage of the total variability due to heterogeneity was estimated with the $\hat{I}^2$ statistic.

Both random and mixed effects models were tested. As moderators, we used the factor "type of nutraceutical" and the covariates "duration of the trial", "year of publication" and "number of dogs in the trial". The different nutraceuticals used in the selected trials were green-lipped mussels (GLM), fish oil, chondroitin sulphate, P54FP, Zeel®, omega-3 fatty acids, and cannabidiol. One trial used a mixture of glucosamine HCl, chondroitin sulphate and hyaluronic acid. P54FP is an extract of Indian and Javanese turmeric, *Curcuma domestica* and *Curcuma xanthorrhiza* respectively, containing a mixture of active ingredients including curcuminoids and essential oils (INNES et al., 2003). Zeel® is the commercial name of a homeopathic preparation.

For the purpose of this meta-analysis, the levels of the factor "type of nutraceutical" considered were GLM and others, due to the variety of nutraceuticals used in the different trials, with GLM being predominant.

The publication bias was evaluated via funnel plot and tested with the regression test (weighted

Table 1: The 13 trials included in the meta-analysis and the variables used as moderators.

Trial	Dogs	Days	Nutr.*
BUI and BIERER, 2001	31	42	GLM†
BIERER and BUI, 2002	96	42	GLM
DOBENECKER et al., 2002-1	37	21	GLM
DOBENECKER et al., 2002-2	40	21	CS‡
INNES et al., 2003	54	22	P54FP§
POLLARD et al., 2006	79	56	GLM
HIELM-BJÖRKMAN et al., 2009a	30	56	GLM
HIELM-BJÖRKMAN et al., 2009b	29	56	Zeel®¶
ROUSH et al., 2010	38	90	Ω-3‖
HIELM-BJÖRKMAN et al., 2012	71	112	DSFO¥
MUREAU et al., 2013	30	91	Ω -3
ALVES et al., 2017	20	152	Mixu
BRIOSCHI et al., 2020	21	84	Can9

*nutraceutical, †green-lipped mussel, ‡chondroitin sulphate §extract of India and Java turmeric *Curcuma domestica* and *Curcuma xanthorrhiza,* ¶commercial name of an homeopathic combination preparation, ‖omega-3 fatty acids, ¥deep sea fish oil, ᵘmixture of glucosamine, chondroitin sulphate and hyaluronic acid, ⁹cannabidiol

regression with multiplicative dispersion). The assumption of normality in the distribution of the residuals was evaluated using a Q-Q normal plot. To assess the consistency of the individual outcomes of the different trials, we used a radial plot. A cumulative meta-analysis was also performed to observe the evolution of the risk factor over time.

The statistical analysis was performed using the freeware R CRAN for Windows® version 4.0.4 platform x86_64-w64-mingw32/x64 (64-bit) (Comprehensive R Archive Network, http://cran.r-project.org/). The specific meta-analysis package "metafor" (VIECHTBAUER, 2010) was used.

Results

A successful random effects model was adjusted ($P<0.001$). The residuals were found to be heterogeneous ($Q=25.5$, $df=12$, $P<0.05$), with $\hat{I}^2=51\%$, but no moderator was found to be significant. The model has an estimate log RR of -0.485 with a 95% confidence interval (CI) of [-0.759; -0.211], or a RR of exp(-0.485) ≈ 0.62 [0.47; 0.81]. The forest plot is presented in Fig. 1.

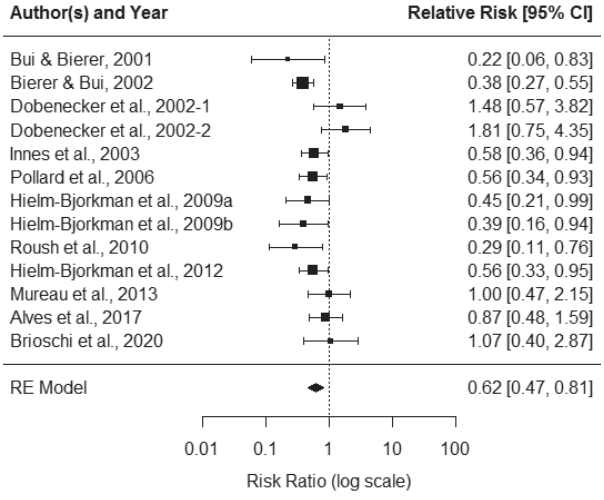

Fig. 1. Forest plot of the adjusted random effects model.

The log of the relative risk or risk ratio (RR) of clinical signs of OA favours nutraceuticals. Therefore, there is evidence confirming the effectiveness of the use of nutraceuticals in the alleviation of the symptoms of canine OA. The cumulative forest plot shown in Fig. 3 shows how the RR has evolved over time. We can see that CIs are growing narrower as result of the increasing sample size and therefore, the accuracy of the prediction improves.

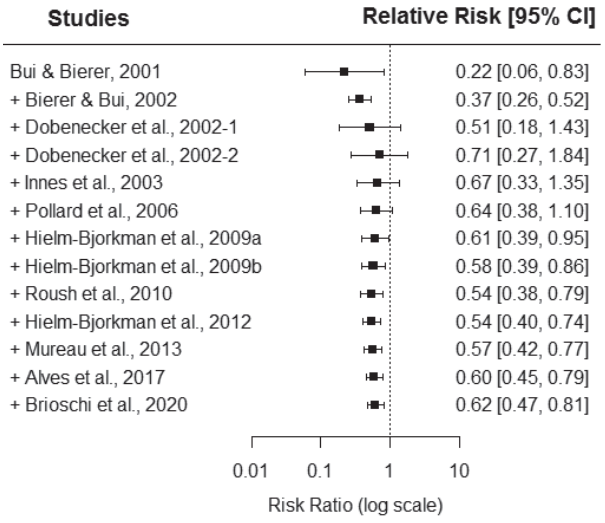

Fig. 2. Cumulative forest plot. The value of the log RR approaches 1 and the confidence interval decreases with time.

Fig. 3 represents the funnel plot for evaluating the publication bias. As can be observed there is comfortable symmetry in the residual distribution to allow the declaration of the non-existence of publication bias. The regression test confirms this ($Z=0.495$, $P=0.62$). We also checked the assumption of the normal distribution of the residuals of the model, which is confirmed by the Q-Q plot in Fig. 4 showing the distribution of the residuals within the 95% confidence envelope. Finally, we assessed and confirmed the consistency of the individual outcomes of the different trials, using a radial plot (Fig. 5).

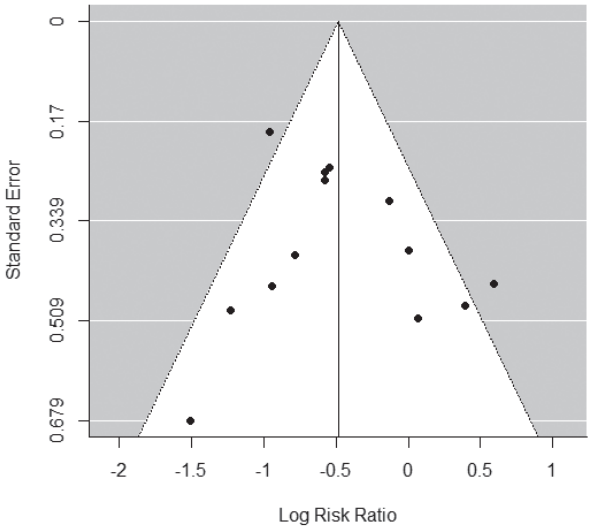

Fig. 3. Funnel plot showing a good symmetry of the residuals of the model, with two small deviations from the 95% pseudo confidence interval.

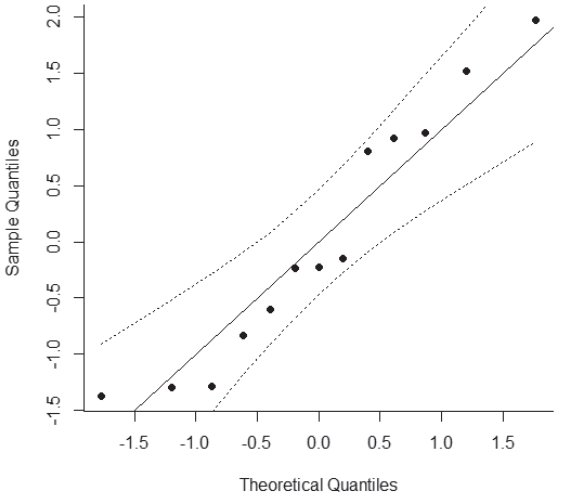

Fig. 4. Q-Q plot showing the distribution of the residuals of the model.

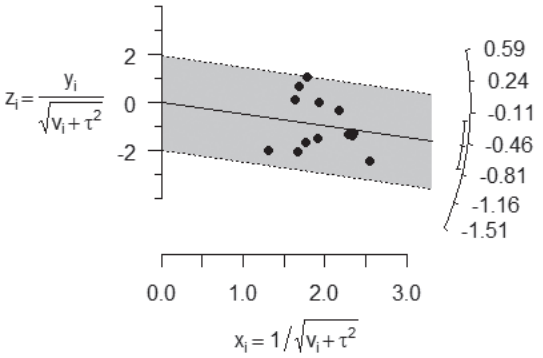

Fig. 5. Radial plot showing the consistency of the individual outcomes of different trials.

Discussion

The green lipped mussel (GLM) (*Perna canaliculus*) and fish oils have very similar pharmacologically active ingredients, including Ω-3 and other long chain fatty acids (ROUSH et al., 2010). These contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that compete for the cyclooxygenase enzyme (COX); synthesis of prostaglandins) and the lipoxygenase enzyme. These two enzymes are involved in the synthesis of the inflammatory agents prostaglandin and leukotriene (TRESCHOW et al., 2007). Therefore, DHA and EPA reduce the levels of these inflammatory agents. The similarities in the active ingredients of the different nutraceuticals used in the trial part of this meta-analysis may explain the lack of significance of the type of nutraceutical in the moderation. In humans, several nutraceuticals have been shown to provide essential components needed to maintain cartilage health (FRECH and CLEGG, 2007). A study conducted by KROMANN and GREEN (1980) looked at the effect of the Inuit Eskimo diet, which is rich in Ω-3 polyunsaturated fatty acids, on the incidence of musculoskeletal disease in the population of the Upernavik district, Greenland. It was found that the incidence of musculoskeletal disease was low in this population due to their diet. There was also a reduced incidence

of heart disease, indicating that nutraceuticals may be beneficial in preventing and treating a number of diseases. A further study conducted in cats found that dietary supplementation with long-chain Ω-3 polyunsaturated fatty acids over a 10-week period was effective at alleviating behavioural and clinical signs of feline OA (CORBEE et al., 2012).

In comparison to GLM and fish oil, little is known about HCP Zeel®, thus further research is necessary to enhance our knowledge on both the nutraceutical effect and safety of that compound. This product contains extracts of plants with anti-inflammatory and anti-microbial properties: *Arnica montana* and *Solanum dulcamara* (anti-inflammatory, *Rhus toxicodendron* (anti-microbial) and *Sanguinaria canadensis* (both) (BIRNESSER and STOLT, 2007).

The treatment option for a dog suffering from OA may be influenced by clinical experience, patient response and the cost of treatment (JOHNSON et al., 2020). Nutraceuticals are relatively inexpensive agents that have the potential to treat a number of diseases as well as helping to maintain normal body systems (LOPEZ, 2012). A multimodal management approach for canine OA that includes the administration of medicinal therapy is likely to be more successful at alleviating the clinical signs of the disease than one management technique used alone (ZHANG et al., 2014; JOHNSON et al., 2020). Current treatment recommendations for OA include a combination of non-pharmacological treatments such as weight loss and exercise, and pharmacological treatments including the use of NSAIDs (JOHNSON et al., 2020).

The duration of the trial was not found to be a significant moderator in this meta-analysis. However, the effects of nutraceuticals are thought to build up over time, therefore it could have been predicted that longer trials yield better results, as suggested by AMEYE and CHEE (2006) in humans. The shortest duration of the trials included in this meta-analysis was 21 days (DOBENECKER et al., 2002). The longest duration of the trials included in this meta-analysis was 157 days (ALVES et al., 2017). Interestingly, the trial of longest duration yielded non-significant results showing that deep-sea fish oil was not effective at alleviating clinical signs of canine OA, whereas the trial of shortest duration yielded significant results showing that GLM was effective at alleviating clinical signs of canine OA. Due to the discrepancies and lack of understanding associated with this concept, long-term trials conducted over a period of months or years may be beneficial in understanding the effects of the long-term use of nutraceuticals. There have been several systematic reviews conducted previously looking into treatment methods for canine OA, including the use of nutraceuticals, therefore a meta-analysis is the logical next step (ARAGON, et al., 2007; SANDERSON et al., 2009, VANDERWEERD et al., 2012).

Meta-analyses are very time consuming and require great effort. Despite an exhaustive search of literature, it is impossible to find every study relevant to the meta-analysis. Although the methodologies of the studies included in this model were very similar, some of the studies only included subjective assessment of pain (*e.g.* BIERER and BUI, 2002; BUI and BIERER, 2001; ROUSH et al., 2010) whereas others used this subjective assessment in combination with an objective methodology using GRFs (HIELM-BJÖRKMAN et al., 2009a; HIELM-BJÖRKMAN et al., 2012). The use of GRFs may provide a standardized means of measuring OA, whereas subjective assessment allows for variation therefore decreasing the internal validity. A limitation of this meta-analysis are the different and unstandardized methodologies used in the different studies, preventing objective comparisons. Therefore, any meta-analysis methodology, including the one used in the present study, may leave out some relevant studies. Nevertheless, we were able to use a significant number of studies conducted over the past 20 years, combining 648 dogs in a single study.

Conclusions

A meta-analysis was conducted to determine the efficacy of nutraceuticals in alleviating clinical signs of canine OA. This study suggests that nutraceuticals are effective at alleviating clinical signs of canine OA. None of the moderators used ("year of publication", "nutraceutical", "duration

of the study" and "number of dogs in the trial") significantly affected the efficacy of nutraceuticals (P>0.05). Further research to assess the long-term efficacy and safety of nutraceuticals is now needed, to understand the long-term effects of these products. Firstly, the efficacy of these drugs may improve in the long-term due to the accumulation of their action over time. Secondly, there is some evidence to suggest that nutraceuticals may be beneficial in preventing musculoskeletal diseases such as OA. This is in addition to a wealth of other diseases, including cardiovascular problems if nutraceuticals are provided throughout the lifetime of the animal. Nutraceuticals are an exciting prospect in the prevention and treatment of OA and other chronic diseases as they are relatively cheap, easy to administer and have no adverse side effects associated with them.

Conflicts of interest

This review results from independent research not supported financially or in any other way. The authors declare the non-existence of conflicts of interest.

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References

ALVES, J. C., A. M. SANTOS, P. I. JORGE (2017): Effect of an oral joint supplement when compared to carprofen in the management of hip osteoarthritis in working dogs. Top. Companion Anim. Med. 32, 126-129.
DOI: 10.1053/j.tcam.2017.10.003

AMEYE, L. G., W. S. S. CHEE (2006): Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. Arthritis Res. Ther. 8, R127.
DOI: 10.1186/ar2016

ANDERSON, K. L., D. G. O'NEILL, D. C. BRODBELT, D. B. CHURCH, R. L. MEESON, D. SARGAN, J. F. SUMMERS, H. ZULCH, L. M. COLLINS (2018): Prevalence, duration and risk factors for appendicular osteoarthritis in a UK dog population under primary veterinary care. Sci. Rep. 4, 5641.
DOI: 10.1038/s41598-018-23940-z

ARAGON, C. L., E. H. HOFMEISTER, S. C. BUDSBERG (2007): Systematic review of clinical trials of treatments for osteoarthritis in dogs. J. Am. Vet. Med. Assoc. 230, 514-521.
DOI: 10.2460/javma.230.4.514

BEYNEN, A. C., E. LEGERSTEE (2010): Influence of dietary beta-1,3/1,6-glucans on clinical signs of canine osteoarthritis in a double-blind, placebo-controlled trial. Am. J. Anim. Vet. Sci. 5, 97-101.
DOI: 10.3844/ajavsp.2010.97.101

BIERER, T. L., L. M. BUI (2002): Improvement of arthritic signs in dogs fed green-lipped mussel (*Perna canaliculus*). J. Nutr. 32, 1634S-6S.
DOI: 10.1093/jn/132.6.1634S

BIRNESSER, H., P. STOLT (2007): The homeopathic antiarthritic preparation Zeel comp. N: A Review of molecular and clinical data. EXPLORE (NY) 3, 16-22.
DOI: 10.1016/j.explore.2006.10.002

BOUND, N. J., M. J. UPJOHN, S. JACKSON, S. J. BAINES (2011): Assessment of veterinary practitioners in the British Isles' approaches towards the management of canine osteoarthritis. Vet. Rec. 168, 563-571.
DOI: 10.1136/vr.d1021

BUCKLAND-WRIGHT, J. C. (1994): Quantitative radiography of osteoarthritis. Ann. Rheum. Dis. 53, 268-275.
DOI: 10.1136/ard.53.4.268

BUDSBERG, S. C., J. W. BARTGES (2006): Nutrition and osteoarthritis in dogs: does It help? Vet. Clin. North. Am. Small. Anim. Pract. 36, 1307-1323.
DOI: 10.1016/j.cvsm.2006.08.007

BUI, L. M., T. L. BIERER (2001): Influence of green lipped mussels (*Perna canaliculus*) in alleviating signs of arthritis in dogs. Vet. Ther. 4, 397-407.

CORBEE, R. J., M. M. C. BARNIER, C. H. A. VAN DE LEST, H. A. W. HAZEWINKEL (2012): The effect of dietary long-chain omega-3 fatty acid supplementation on owner's perception of behaviour and locomotion in cats with naturally occurring osteoarthritis. J. Anim. Physiol. Anim. Nutr. 97, 846-853.
DOI: 10.1111/j.1439-0396.2012.01329.x

D'ALTILIO, M., A. PEAL, M. ALVEY, C. SIMMS, A. CURTSINGER, R. C. GUPTA, T. D. CANERDY, J. T. GOAD, M. BAGCHI, D. BAGCHI (2007): Therapeutic efficacy and safety of undenatured type II collagen singly or in combination with glucosamine and chondroitin in arthritic dogs. Toxicol. Mech. Method. 17, 189-196.
DOI: 10.1080/15376510600910469

DOBENECKER, B., Y. BEETZ, E. KIENZLE (2002): A placebo-controlled double-blind study on the effect of nutraceuticals (chondroitin sulfate and mussel extract) in dogs with joint diseases as perceived by their owners. J. Nutr. 132, 1690S-1S.
DOI: 10.1093/jn/132.6.1690S

FRANKLIN, S. P., R. D. PARK, E. L. EGGER (2009): Metacarpophalangeal and metatarsophalangeal osteoarthritis in 49 dogs. J. Am. Anim. Hosp. Assoc. 45, 112-117.
DOI: 10.5326/0450112

FRECH, T. M., D. O. CLEGG (2007): The utility of nutraceuticals in the treatment of osteoarthritis. Curr. Rheumatol. Rep. 9, 25-30.
DOI: 10.1007/s11926-007-0018-x

FRITSCH, D., T. A. ALLEN, C. E. DODD, D. E. JEWELL, K. A. SIXBY, P. S. LEVENTHAL, K. A. HAHN (2010): Dose-titration effects of fish oil in osteoarthritic dogs. J. Vet. Intern. Med. 24, 1020-1026.
DOI: 10.1111/j.1939-1676.2010.0572.x

FOX, S. M. (2007): NSAIDs and nutraceuticals: What's the evidence? Proceedings of the Western Veterinary Conference, 7 July, Las Vegas, USA.

GUPTA, R. C., T. D. CANERDY, J. LINDLEY, M. KONEMANN, J. MINNIEAR, B. A. CARROLL, C. HENDRICK, J. T. GOAD, K. ROHDE, R. DOSS, M. BAGCHI, D. BAGCHI (2011): Comparative therapeutic efficacy and safety of type-II collagen (uc-II), glucosamine and chondroitin in arthritic dogs: pain evaluation by ground force plate. J. Anim. Physiol. Anim. Nutr. 96, 770-777.
DOI: 10.1111/j.1439-0396.2011.01166.x

HENROTIN, Y., C. SANCHEZ, M. BALLIGAND (2005): Pharmaceutical and nutraceutical management of canine osteoarthritis: Present and future perspectives. Vet. J. 170, 113-123.
DOI: 10.1016/j.tvjl.2004.08.014

HIELM-BJÖRKMAN, A., J. ROINE, K. ELO, A. LAPALAINEN, J. JUNNILA, L-V. OUTI (2012): An uncommissioned randomized, placebo-controlled double-blind study to test the effect of deep sea fish oil as a pain reliever for dogs suffering from canine OA. BMC Vet. Res. 8, 157-170.
DOI: 10.1186/1746-6148-8-157

HIELM-BJÖRKMAN, A., R. M. TULANO, H. SALONEN, M. RAEKALLIO (2009a): Evaluating complementary therapies for canine osteoarthritis part I: Green-lipped mussel (*Perna canaliculus*). Evid. Based Complement. Altern. Med. 6, 365-373.
DOI: 10.1093/ecam/nem136

HIELM-BJÖRKMAN, A., R. M. TULANO, H. SALONEN, M. RAEKALLIO (2009b): Evaluating Complementary Therapies for Canine Osteoarthritis—Part II: A Homeopathic Combination Preparation (Zeel®), Evid. Based Complement. Altern. Med. 6, 465-471.
DOI: 10.1093/ecam/nem143

IMHOFF, D. J., W. J. GORDON-EVANS, R. B. EVANS, A. L. JOHNSON, D. J. GRIFFON, K. S. SWANSON (2011): Evaluation of *s*-adenosyl l-methionine in a double-blinded, randomized, placebo-controlled, Clinical trial for treatment of presumptive osteoarthritis in the dog. Vet. Surg. 40, 228-232.
DOI: 10.1111/j.1532-950X.2010.00788.x

INNES, J. F., J. CLAYTON, B. D. X. LASCELLES (2010): Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. Vet. Rec. 166, 226–230.
DOI: 10.1136/vr.c97

INNES, J. F., C. J. FULLER, E. R. GROVE, A. L. KELLY, J. F. BURN. (2003): Randomised, double-blind, placebo-controlled parallel group study of P54FP for the treatment of dogs with osteoarthritis. Vet. Rec. 152, 457-460.
DOI: 10.1136/vr.152.15.457

JOHNSON, K. A., A. H. LEE, K. S. SWANSON (2020): Nutrition and nutraceuticals in the changing management of osteoarthritis for dogs and cats. J. Am. Vet. Med. Assoc. 15, 1335-1341.
DOI: 10.2460/javma.256.12.1335

KAHN, C. M. (2010): The Merck veterinary manual. 10th ed., Merck & Co. Inc, Rahway, pp. 64-85.
DOI: 10.1111/j.1439-0396.2011.01166.x

KROMANN, N., A. GREEN (1980): Epidemiological studies in the Upernavik district, Greenland. Incidence of some chronic diseases 1950-1974. Acta Med. Scand. 208, 401-406.

LOPEZ, H. L. (2012): Nutritional interventions to prevent and treat osteoarthritis. Part II: Focus on micronutrients and supportive nutraceuticals. PM&R 4, S155-168.
DOI: 10.1016/j.pmrj.2012.02.023

MOUREAU, M., B. LUSSIER, M. DOUCET, G. VINCENT, J. MARTEL-PELLETIER, J.-P. PELLETIER (2007): Efficacy of licofelone in dogs with clinical osteoarthritis. Vet. Rec. 160, 584-588.
DOI: 10.1136/vr.160.17.584

MOUREAU, M., J. DUPUIS, N. H. BONNEAU, M. DESNOYERS (2003): Clinical evaluation of a nutraceuticals, carprofen and meloxicam for the treatment of dogs with osteoarthritis. Vet. Rec. 152, 323-329.
DOI: 10.1136/vr.152.11.323

POLLARD, B., W. G. GUILFORD, K. L. ANKENBAUER-PERKINS, D. HEDDERLEY (2006): Clinical efficacy and tolerance of an extract of green-lipped mussel (*Perna canaliculus*) in dogs presumptively diagnosed with degenerative joint disease. N. Z. Vet. J. 54, 114-118.
DOI: 10.1080/00480169.2006.36622

PUCHEU, B., B. DUHAUTOIS (2009): Multicentric, randomized and positive-controlled study to assess the efficacy of an association of chondroitin sulphate, chitosan, l-selenomethionine and epigallocatechin-3-gallate in the control of osteoarthritis and functional postoperative recovery. Prat. Med. Chir. Anim. Comp. 44, 35-44.
DOI: 10.1016/j.anicom.2009.03.001

ROUSH, J. K., C. E. DODD, D. A. FRITSCH, T. A. ALLEN, D. E. JEWELL, W. D. SCHOENHERR, D. C. RICHARDSON, P. S. LEVENTHAL, K. A. HAHN (2010): Multicenter veterinary practice assessment of the effects of omega-3 fatty acids on osteoarthritis. J. Am. Vet. Med. Assoc. 236, 59-66.
DOI: 10.2460/javma.236.1.59

RYCHEL, J. K. (2010): Diagnosis and treatment of osteoarthritis. Top. Companion Anim. Med. 25, 20-25.
DOI: 10.1053/j.tcam.2009.10.005

SANDERSON, R. O., C. BEATA, R-M. FLIPO, J-P. GENEVOIS, C. MACIAS, S. TACKLE, A. VEZZONI, J. F. INNES (2009): Systematic review of the management of canine osteoarthritis. Vet. Rec. 164, 418-424.
DOI: 10.1136/vr.164.14.418

TEIXEIRA, L. R., S. P. LUNA, L. M. MATSUBARA, M. L. CÁPUA, B. P. SANTOS, L. R. MESQUITA, L. G. FARIA, F. S. AGOSTINHO, A. HIELM-BJÖRKMAN (2016): Owner assessment of chronic pain intensity and results of gait analysis of dogs with hip dysplasia treated with acupuncture. J. Am. Vet. Med. Assoc. 1, 1031-1039.
DOI: 10.2460/javma.249.9.1031

TRESCHOW, A. P., L. D. HODGES, P. F. A. WRIGHT, P. M. WYNNE, N. KALAFATIS, T. A. MACRIDES (2007): Novel anti-inflammatory w-3 PUFAs from the New Zealand green-lipped mussel, *Perna canaliculus*. Comp. Biochem. Phys. B. 147, 645-656.
DOI: 10.1016/j.cbpb.2007.04.004

VANDERWEERD, J-M., C. COISNON, P. CLEGG, C. CAMBIER, A. PIERSON, F. HONTOIR, C. SAEGERMAN, P. GUSTIN, S. BUCZINSKI (2012): Systematic review of efficacy of nutraceuticals to alleviate clinical signs of osteoarthritis. J. Vet. Intern. Med. 26, 448-456.
DOI: 10.1111/j.1939-1676.2012.00901.x

VIECHTBAUER, W. (2010): Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36, 1-48.
DOI: 10.18637/jss.v036.i03

ZHANG, R., L. LIXING, K. REN, B. M. BERMAN (2014): Mechanisms of acupuncture–electroacupuncture on persistent pain. Anesthesiol. 120, 482–503.
DOI: 10.1097/ALN.0000000000000101

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SAŽETAK

Osteoartritis je često stanje u pasa. Trenutačno se u liječenju najčešće upotrebljavaju nesteroidni portuupalni lijekovi, no njihova kontinuirana primjena može uzrokovati brojne teške nuspojave, uključujući i smrt. Stoga se povećava zanimanje za alternativne načine liječenja, pri čemu su nutraceutici od temeljne važnosti. U navedenom području proveden je niz pojedinačnih istraživanja i sustavnih pregleda ali još uvijek nije provedena njihova metaanaliza. Ovim istraživanjem nastoji se popuniti ta praznina, pri čemu su kombinirani rezultati 13 istraživanja parova uz uporabu placeba. Uključeno je ukupno 638 pasa od kojih je 327 liječeno nutraceuticima, dok je 321 pas poslužio kao kontrola. Uspješno prilagođavanje modela slučajnih učinaka ($P<0,001$) provedeno je s omjerom rizika od 0,62 unutar 95 % CI od [0,47; 0,81] u korist nutraceutika. Nutraceutici upotrijebljeni u istraživanjima bili su zelena dagnja, hondroitin-sulfat, ekstrakt indijske i javanske kurkume (P54FP), homeopatska kombinacija preprarata poznatog kao Zeel®, omega-3 masne kiseline, ulje ribe iz dubokih mora, mješavina glukozamina s hondroitin-sulfatom i hijaluronskom kiselinom te kanabidiol.

Ključne riječi: metoda istraživanja parova; osteoartritis u pasa; metaanaliza; nutraceutici; smanjenje boli