Review
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Systematic Review of Efficacy of Nutraceuticals to Alleviate Clinical Signs of Osteoarthritis

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Background: Various treatments of osteoarthritis (OA) have been described, including use of nutraceuticals.

Objectives: To review systematically the literature about the effects of nutraceuticals on clinical signs of pain or abnormal locomotion in horses, dogs, and cats, and to discuss methodological aspects of trials and systematic reviews.

Methods: A systematic search of controlled trials evaluating the impact of nutraceuticals on OA in horses, dogs, and cats was performed, using Medline, CAB Abstracts, and Google Scholar. Scientific evidence was evaluated by means of criteria proposed by the Food and Drug Administration (FDA), and a scoring system adapted from both the CONsolidated Standards of Reporting Trials (CONSORT) statement and recommendations for assessing trials by the Center of Evidence Based Medicine of Oxford.

Results: Twenty-two papers were selected and reviewed, with 5 studies performed in horses, 16 in dogs, and 1 in cats. The strength of evidence was low for all nutraceuticals except for omega-3 fatty acid in dogs. There were limited numbers of rigorous randomized controlled trials and of participants in clinical trials.

Conclusions and Clinical Importance: The evidence of efficacy of nutraceuticals is poor, with the exception of diets supplemented with omega-3 fatty acids in dogs. Greater access to systematic reviews must be part of the objectives of the veterinary science in the future. Their reporting would be improved by internationally agreed-upon criteria for standards and guidelines.

Key words: Dietary supplements; EBM; Evidence; Locomotion.

Osteoarthritis (OA) is a degenerative and inflammatory condition in which there is a loss of cartilage matrix. It is a particularly prevalent cause of lameness and an expensive equine health problem.[1] It is also a common disease of dogs.[2] Clinically, animals with OA present with stiffness or lameness. Lameness is because of a combination of joint pain and restricted movement of the joint. There are many medical therapeutic options. Corticosteroid, polysulfated glycosaminoglycans, or hyaluronic acid injections are frequently used in horses.[3] In both small animals and horses, nonsteroidal anti-inflammatory drugs are the basic treatment and are most commonly administered PO.[4–6]

Products called "nutraceuticals" have recently appeared on the market. The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 and was defined as "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease."[7] However, the term nutraceutical as commonly used in marketing has no regulatory definition.[8] Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the term "dietary supplement" is defined as a product taken by mouth that contains a "dietary ingredient"

Abbreviations:

OA	osteoarthritis
FDA	Food and Drug Administration
NAVNC	North American Veterinary Nutraceutical Council
EBM	evidence-based medicine
DSHEA	Dietary Supplement Health and Education Act
UC-II	undenatured type II collagen
GLU	glucosamine
CS	chondroitin sulfate
MA	myristoleic acid
MSM	methylsulfonylméthane
HC	hydrolyzed collagen
AOV	amino acids, oligo-element, and vitamins
ASU	avocado and soybean unsaponifiable
β G	β-1,3/1,6 glucans
GH	gelatine hydrolysate
O3FA	omega-3 fatty acids
EPA	eicosopentanoic acid
DHA	docosahexaenoic acid
ETA	eicosatetraenoic acid
HCA	hydroxycitric acid
CMN	chromium nacinate
GLMP	green lipped mussel powder
MN	manganese
SMPC	special milk protein concentrate
P54FP	Indian and Javanese turmeric

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intended to supplement the diet. The "dietary ingredients" in these products can include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, and metabolites. Dietary supplements can also be extracts or concentrates, and can be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders.[9] These different definitions concern human consumers and not pets. According to the North American Veterinary Nutraceutical Council (NAVNC), a nutraceutical is "a substance produced in purified or extracted form which, when administered orally to patients, aims to provide them the necessary elements for their structure and normal function to better their health and well-being,"[10] but this definition has no regulatory meaning. In Europe, no specific indications can be legally recognized for nutraceuticals as no official evidence of efficacy is required to market them and manufacturers do not have to conduct the extensive studies that are necessary to obtain official approval for marketing medicinal products like antibiotics or anti-inflammatories.[11]

The veterinary profession has ethical obligations to ensure effective and safe service and to base therapeutic decisions on scientific evidence.[12–14] Because OA has important clinical consequences on animals, it is important to know the efficacy of products, such as nutraceuticals, that are used in veterinary medicine.

Although evidence-based medicine (EBM) might logically help veterinarians make more informed decisions, obstacles to its widespread adoption have been reported, including the lack of high quality patient-centered research,[15–18] and the inadequacy of EBM tools to the busy daily practice because of the limited time available to veterinarians to keep up to date with the large quantity of scientific literature.[14,19] Other authors have suggested that, as in human medicine, information such as systematic reviews should be available so that practitioners devote their scarce reading time to selected quality scientific information.[20] Systematic reviews are still not common in veterinary medicine. In human medicine, their reporting has been standardized.[21]

The objectives of this study were to review the literature about the usefulness of nutraceuticals for improving clinical signs of pain or abnormal locomotion in horses, dogs, and cats with OA, to illustrate the issue of lack of scientific information about this topic, and to suggest a general methodology of conducting and reporting a systematic review that would improve transparency both for scientists and veterinary practitioners.

Material and Methods

Literature Search

The main investigator conducted a document search using Medline, CAB Abstracts, and Google Scholar databases. With Medline, no "MESH term" (Medical Subject Headings term) was identified for "Nutraceuticals." Instead "Dietary Supplements" was proposed. It was also noticed that common nutraceuticals such as chondroitin sulfate (CS), glucosamine (GLU), and omega-3 fatty acids (O3FA) were not included in the MESH term "Dietary supplements." The descriptors "Chondroitin," "Glucosamine," and "Fish Oils" were therefore added to the search. The following equation was used in Medline: ["Dietary Supplements" OR "Fish Oils" OR "Chondroitin" OR "Glucosamine"] AND ["Osteoarthritis" OR "Joint Diseases"] AND ["Dogs" OR "Cats" OR "Horses"]). Similar terminology was used in CAB Abstracts and Google Scholar (["Nutraceuticals" OR "Dietary Supplements" OR "Fish Oils"] AND ["Osteoarthritis" OR "Joint Diseases"] AND ["Dogs" OR "Cats" OR "Horses"]). In order to identify other studies and to confirm the effectiveness of our study, published reviews focusing on treatment of OA in dogs[5,6] and horses[22,23] were consulted. We also used a more general query ([Trials] AND ["Dogs" OR "Cats" OR "Horses"] AND ["Osteoarthritis" OR "Joint Diseases"]).

Inclusion and Exclusion Criteria for the Articles

Only controlled experimental studies or clinical trials published in English or French before December 2010 were included. To be eligible, the articles had to cover the effects of oral supplements of one or more natural substances in the form of granulated, drinkable solution, capsule, or feed. This criterion was based on the NAVNC's definition of nutraceuticals and aimed to exclude studies on the therapeutic effects of injectable substances.[10] Only in vivo studies evaluating clinical signs of pain or abnormal locomotion were considered. When selection criteria could not be assessed from the abstract, the full article was consulted. As a result of the limited number of clinical studies available in horses, the results obtained from experimental studies on induced OA in this species were included in the review, although their conclusions are less able to be generalized than those obtained from controlled trials in naturally occurring OA.

Assessment of Quality of Publications

As in other systematic reviews already published on the treatment of OA,[5,6] we based our system of evaluation on the one proposed by the Food and Drug Administration (FDA).[24] It included an evaluation of internal validity (step 1) and of external validity (steps 2 and 3). The statistical significance of the effect (step 4) and global level of evidence (step 5) were determined. However, in the FDA system, criteria for the methodological quality of trials (step 1) lack the transparency that is fundamental for evaluation. This system describes quality criteria in general terms: the quality of a study is high if it adequately considered factors such as inclusion/exclusion, bias, ability to generalize, and data collection and analysis; it is intermediate if there are some uncertainties relating to whether the report adequately considered the above factors; it is poor if the study did not adequately address the above factors.

In step 1 in this study, we used several resources to elaborate evaluation criteria and scores: the Consort Statement (CONsolidated Standards of Reporting Trials)[25] and the recommendations for assessing trials described by the Center of Evidence Based Medicine of Oxford (http://www.cebm.net/index.aspx?o=1157). On this basis, 5 persons including 2 clinicians (JMV and SB), an epidemiologist (CS), 2 pharmacotherapists and experts in clinical trials (CC and PG) generated questions and gave a maximum score (weight) for each of them. For example, the questions, referring to the title, "Is identification of the study design present in the title?" and "Is a structured summary of trial design, methods, results, and conclusions provided?" were weighted 1% each. A Delphi process was used to gain consensus among these 5

individuals. This is a group facilitation technique that is interactive and multistage, designed to transform opinion into group consensus.[26] The list of question items was subsequently submitted to 1 bachelor's student and 1 scientist for wording and understanding. A final chart was designed (Table 1). Every publication was evaluated by 2 researchers who gave a score for every item. When discordance occurred, the point was discussed until a consensus was reached. The maximum possible score of quality was 100%. Studies were of high, intermediate, and low quality, if their scores were respectively higher than 60%, between 45 and 60%, and below 45%.

In step 2, the quantity of published information was evaluated on the basis of the number of studies published and the number of individuals tested. Because only 1 or 2 studies cannot reasonably be considered a significant quantity, and the highest number of different publications about the same nutraceutical, among those identified in this review, was only 4, it was arbitrarily decided that a minimum of 3 studies was adequate; 25 animals per group were considered an adequate sample size on the basis of a previous controlled trial, where the number of dogs required was calculated to detect a 10% difference in peak vertical force (measured with a force-plate) between the active treatment and placebo with a power of 80%.[27] Globally, quantity was adequate when the number of studies was superior to 3, and the number of tested animals was equal or superior to 25 in each group (treatment and control). All other situations were considered inadequate.

In step 3, the consistency of results was assessed, that is, whether conclusions of different studies about one substance highlighted a similar effect, either through an improvement or an absence of effect. Consistency was adequate when all studies indicated a similar effect of treatment, or inadequate if they did not

Table 1. Question items used to assess the quality of the methodology in selected studies.

Title and summary (2/100)
Title and abstract: identification of the study design in the title is present (1%); structured summary of trial design, methods, results, and conclusions is provided (1%)
Introduction (2/100)
Background and objectives: scientific background and explanation of rationale are explained (1%); specific objectives or hypotheses are explained (1%)
Material and methods (48/100)
Trial design: the trial is controlled (1%) and allocation ratio is described (1%); reference is made to an ethical protocol (1%)
Participants: eligibility criteria for participants (2%), settings, locations where the data were collected (2%), inclusion criteria (2%), exclusion criteria (2%) are detailed
Interventions: the interventions for each group are described with sufficient details to allow replication (5%) and no additional treatment is allowed (2%)
Outcomes: subjective outcome measures are used and accurately described (2%); semiobjectives measures are used (2%); objective outcome measures are used (2%)
Sample size: how the sample size was determined is reported (3%)
Randomization: allocation is randomized (2%), method used to generate the random allocation sequence is described (4%); details of restriction are reported (1%)
Allocation concealment: mechanism used to implement the random allocation sequence and to conceal the sequence until intervention is described (2%)
Implementation: it is reported who generated the random allocation sequence, who enrolled participants, and who assigned participants to the interventions (1%)
Blinding: blinding is present (2%) with description of who was blinded after assignment to interventions and how blinding was performed (2%)
Placebo: a placebo was used (2%)
Statistical methods: statistical methods are accurately described (5%)
Results (30/100)
Flux of participants: the numbers of participants who were eligible, included or excluded, randomly assigned, received intended treatment, lost to follow-up and analyzed for the primary outcome are described (2%) in a flow chart or table (2%), reasons are explained (2%), and less than 20% of patients are lost to follow-up (2%)
Recruitment: dates defining the periods of recruitment and follow-up are reported (3%)
Baseline data: a table showing baseline demographic characteristics for each group is presented with treated and control groups similar at the start of the trial (8%)
Subjects analyzed: it is reported whether the results were analyzed by Intention to Treat or Per Protocol (3%)
Results: results for each group were accurately described (3%)
Analyses: results of any analyses are explained (2%); the effect size and clinical significance are reported (1%)
Risks: all important harms or unintended effects in each group are adequately explained (2%)
Discussion (15/100)
Limitations: trial limitations, sources of potential bias, imprecision, and, if relevant, multiplicity of analyses, are addressed (5%)
Generalizability: generalizability (external validity, applicability) of the trial findings is discussed (5%)
Interpretation: interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence, are provided (5%)
Additional information (3/100)
Funding: funding sources and other supports (for example pharmaceutical firms) (1%) are mentioned, and absence or presence of conflicts of interest is declared (2%)

This scale was elaborated from the CONSORT statement and recommendations of the Center of Evidence Based Medicine of Oxford. A score (in percentage) is given for each item question and the sum of each score reflects the quality of the paper.

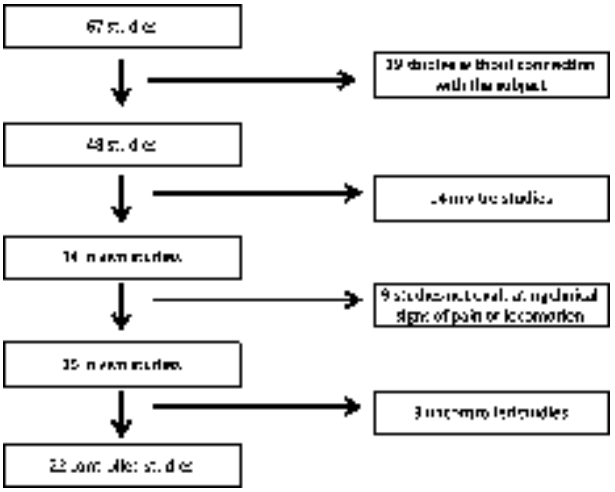

Fig 1. Flow of information through the different phases of this systematic review.

meet this criterion. When the effects of 1 substance were studied in only 1 trial, the consistency could not be evaluated; therefore the abbreviation "NA" (nonapplicable) was used in the results chart.

In step 4, it was considered whether the studies demonstrated a statistically significant effect or not (change in outcome measure).

Step 5 aimed to obtain a global strength of evidence provided by the studies on a given nutraceutical, that is, whether there were low or strong indications for clinical use of the product in order to improve clinical signs of pain or abnormal locomotion in OA. Indications were strong when there was adequate quantity and consistency of high or intermediate quality studies demonstrating a significant effect. They were low in all other situations.

Results

Through our searches, we were able to identify a total of 67 eligible studies; however, only 22 studies fulfilled the criteria.[4,27–47] Forty-five studies were not selected for several reasons that are detailed in Figure 1. Two of the 22 studies were performed in a horse model of OA.[30,31] The key properties of studies are reported in Table 2. The detailed results of quality assessment (step 1) can be accessed online (Addendum), whereas the total scores of quality (step 1) and the results of steps 2–5 are reported in Table 3.

In horses, soybean and avocado unsaponifiables (ASU) extracts had no effect.[30] and global strength of

Table 2. Key features of selected studies. Each study has an ID (identity) number and its publication is referenced (Ref).

ID	Ref	Species	Supplement	Design	N	Duration	Outcome Measures	Funding
1	28	Horse	UC-II GLU and CS	NRCT, PBO, NOA	25	150	SOA	Y
2	29	Horse	Compound (MA, GLU, MSM, AOV)	RCT, DB, PBO, NOA	40	28	SOA	Y
3	30	Horse	ASU	RCT, DB, PBO, MOA	16	70	SOA	Y
4	31	Horse	Low molecular weight CS Native CS	RCT, DB, PBO, MOA	10	70	SOA	N
5	32	Horse	AOV	RCT, DB, PBO,NOA	8	14	OA	Y
6	33	Dog	βG	RCT, DB, PBO, NOA	46	56	SUA	N
7	34	Dog	GH	RCT, DB, PBO, NOA	60	56	SUA	N
8	35	Dog	O3FA	RCT, DB, NOA	177	90	SOA, SUA	Y
9	36	Dog	O3FA	RCT, DB, NOA	131	90	SOA, SUA	N
10	37	Dog	O3FA	RCT, DB, NOA	127	180	SUA	N
11	38	Dog	O3FA	RCT, DB, NOA	38	90	SOA, SUA, OA	N
12	39	Dog	UC-II HCA Combinations with CM	RCT, DB, PBO, NOA	25	120	SUA	Y
13	40	Dog	Compound (GLU, CS)	RCT, DB, PBO, NOA	35	70	SOA	Y
14	41	Dog	GLMP	RCT, DB, PBO, NOA	81	56	SOA, SUA	Y
15	42	Dog	GLMP	RCT, DB, NOA	96	42	SOA	Y
16	43	Dog	GLMP	RCT, DB, NOA	31	42	SOA	Y
17	44	Dog	GLMP CS	RCT, DB, PBO, NOA	58	84	SOA, SUA	N
18	45	Dog	Compound (GLU, CS, MN)	RCT, DB, PBO, NOA	71	60	SOA, SUA, OA	Y
19	46	Dog	UC-II	RCT, DB, PBO, NOA	15	90	SUA	Y
20	4	Dog	SPMC	RCT, DB, PBO, NOA	35	56	SOA, SUA	Y
21	24	Dog	P54FP	RCT, DB, PBO, NOA	54	56	SOA, SUA, OA	Y
22	47	Cat	Compound (O3FA, GLMP, GLU, CS)	RCT, DB, NOA	40	70	SOA, SUA, OA	Y

Gupta et al 2009,[28] Keegan et al 2007,[29] Kawcak et al 2007,[30] Verde et al 2006,[31] Clayton et al 2002,[32] Beynen et al 2010,[33] Beynen et al 2010,[34] Fritsch et al 2010,[35] Fritsch et al 2010,[36] Roush et al 2010,[37] Roush et al 2010,[38] Peal et al 2007,[39] McCarthy et al 2007,[40] Pollard et al 2006,[41] Bierer et al 2002,[42] Bui et al 2001,[43] Dobenecker et al 2002,[44] Moreau et al 2003,[45] Deparle et al 2005,[46] Gingerich et al 2003,[4] Innes et al 2003,[27] Lascelles et al 2010.[47]

Several supplements are compared and when they are administered simultaneously to the same animal they are called a compound. The trials can be randomized (RCT) or not (NRCT), placebo controlled (PBO), and double blinded (DB). Supplements were tested in naturally occurring OA (NOA) in horses, dogs and cats, but also in models of OA (MOA) in horses. The number of animals (N) included and the duration of treatments (in days) are reported. Three types of outcome measures were identified: either subjective (SUA, eg, owner's opinion), semiobjective (SOA, eg, clinical test performed by a veterinary surgeon), or objective (OA, eg, force plate). Studies can be supported by sponsors or funded (Y) or not (N).

Table 3. Summary of steps 1–5.

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Reference	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	4	27	47
	Horse												Dog									Cat
Quality	41 Lo	55 In	49 In	44 Lo	48 In	48 In	46 In	74 Hi	68 Hi	57 In	59 In	24 Lo	67 Hi	58 In	27 Lo	44 Lo	40 Lo	65 Hi	44 Lo	63 Hi	83 Hi	74 Hi
Quantity	Ina	Ina	Ina	Ina	Ina	Ina	Ina	Adequate				Ina	Ina	Adequate				Ina	Ina	Ina	Ina	Ina
Significance	S	S	NS	S	S	S	S	S	S	S	S	Va	S	S	S	S	NS	NS	S	S	Vo	S
Consistency	NA	NA	NA	NA	NA	NA	NA	Adequate				NA	NA	Inadequate				NA	NA	NA	NA	NA
Global strength	Lo	Lo	Lo	Lo	Lo	Lo	Lo	Hi				Lo	Lo	Lo				Lo	Lo	Lo	Lo	Lo

The results of quality assessment (step 1, table 1) are reported in this table: studies are of high, intermediate or low quality. In step 2, the quantity of studies referring to the same nutraceutical was either adequate or inadequate (Ina). In step 3, it was assessed whether the administration of the nutraceutical had a significant (S) or non significant (NS) effect. In studies where several nutraceuticals were assessed and a significant effect could be demonstrated for some of them but not for others, the result was noted Va (variable result). It is the case for the study of Peal et al[39] where all nutraceuticals had a significant effect except HCA. For the study of Innes et al,[27] the significance is noted Vo (variable outcome) as the results are not significant for objective (force-plate) and subjective (owner's opinion) outcomes but significant for semi-objective outcomes (clinical examination). In step 4, the consistency is either adequate (Ade) or inadequate (Ina). It is non-applicable (NA) when only one study has been performed. In step 5, the global evidence was either strong (ST) or low (LO).

evidence of efficacy was low for non-denatured type II collagen (UC-II)[28]; CS[31]; combinations of oligo-elements, amino acids, and vitamins (AOV)[32]; and combinations of myristoleic acid (MA), GLU, methylsulfonylmethane (MSM), hydrolyzed collagen (HC), and AOV.[29]

In dogs, hydroxycitric acid (HCA)[39] and extract of Indian and Javanese turmeric (P54FP)[27] were not effective, although for the latter veterinarians reported an improvement in clinical signs in contradiction with objective data that were obtained with a force plate. Global strength of evidence of efficacy was low in studies demonstrating a significant effect for the use of β-1,3/1,6 glucans (β G)[33]; gelatine hydrolysate (GH)[34]; UC-II alone or combined with HCA or with chromium nacinate (CMN)[39]; special milk protein concentrate (SMPC).[4] Two different compounds containing GLU and CS showed contradictory results: one compound had beneficial effects,[40] although the other one (combined with manganese [MN]) had no effect.[45] The highest global strength of evidence of efficacy was demonstrated by O3FA supplemented diets.[35–38] Green lipped mussel powder (GLMP) had a significant effect in 3 of 4 studies,[41–44] and because of this inconsistency between studies, we could not conclude to a strong indication for its clinical use.

In cats, it was not possible to recommend the use of diets supplemented with O3FA, GLMP, GLU, and CS,[47] as only 1 study, though of high quality, had been performed for this product.

This review identified several major methodological issues in clinical trials: the limited numbers of rigorous randomized controlled trials and of patients in studies, the lack of objective outcome measures, the uncommon use of the concept of "effect size," the risk of conflict of interest, the lack of standardization of dosages and duration of treatments.

Discussion

In this review, it is the potential of nutraceuticals to alleviate the clinical signs of OA that was evaluated, rather than any potential disease (structure)-modifying effects. Only clinical and in vivo experimental studies were selected. This does not mean that we considered in vitro studies as being of low quality. Their conclusions are simply less easy to generalize to the population of animals and are less useful to answer clinical questions referring to improvement of signs of pain and abnormal locomotion.

We found 4 randomized controlled trials in dogs concerning diets supplemented with O3FA, which were of high quality and demonstrated a significant effect on clinical signs of OA.[35–38] A meta-analysis in humans found that dietary supplementation with fish oil, which is enriched in O3FA, especially eicosopentanoic acid (EPA) and docosahexaenoic acid (DHA), provides benefits in rheumatoid arthritis. O3FA may lower arachidonic acid concentrations and alter the production of eicosanoids to less inflammatory forms.[48] In addition, O3FA would reduce the expres-

sion of cartilage degrading enzymes, cyclooxygenase-2, and inflammation-inducible cytokines.[49]

Although, in dogs, no effect with GLMP-enriched diet was reported,[44] 3 other studies demonstrated a significant improvement of the outcome measures in the tested group versus the control group in this species. According to this inconsistency, we could not recommend the use of GLMP in OA. However, the reason for which no effect was observed in the 1st study might be because of the dose administered, which was only 10 mg of GLMP per day and per kg,[44] whereas dogs received between 20 mg and 100 mg per day and per kg in the other studies.[41–43] Dosage should be standardized to compare nutraceuticals objectively. Moreover, a high quality study in cats demonstrated a beneficial effect of a diet supplemented with O3FA, GLU, and GLMP.[47] GLMP has been shown to contain a unique O3FA, eicosatetraenoic acid (ETA), which appears to act as dual inhibitor of arachidonic acid oxygenation by both the cyclooxygenase and lipoxygenase pathways.[50] Other controlled clinical trials should be done to establish a link between O3FA and GLMP because the effect of GLMP might be at least partly because of O3FA.[50]

P54FP, an extract of Indian and Javanese turmeric, contains a mixture of active ingredients including curcuminoids and essential oils and has been reported to possess anti-inflammatory properties.[51] ASU has shown, in vitro, positive effect on both the inflammatory cascade and structural components of articular cartilage matrix.[52,53] In the identified studies, the administration of P54FP in dogs and ASU in horses resulted in no change in objective outcome measures of clinical signs of OA.[27,30] Interestingly, results suggest that the ASU extracts can induce structural modification of the joint surface. This illustrates that nutraceuticals might be beneficial in the management of OA by reducing the progression of gross articular cartilage damage, although other methods for improving clinical signs would need to be used.[30]

GLU and CS are nutraceuticals that are commonly used as dietary supplements in several species. There are indications that they provide prophylactic protection against synovitis,[54] they retard the degenerative process synergistically[55] and they modulate the metabolism of articular cartilage.[56] According to our criteria in this review, the global strength of evidence of efficacy was low for GLU and CS. In addition, results were contradictory in the 2 studies conducted in dogs[40,45] and, in one of 3 studies performed in horses[29] and in the only one performed in cats,[47] GLU and CS were part of a compound including other nutraceuticals that might have been responsible for the clinical effect as well.

Different mechanisms of action and properties have been reported for other nutraceuticals that were tested in the studies identified for this review (UC-II, β G, MA, MSM, and SPMC). The effect of AOV[32] and HCA[39] was evaluated without real explanation of their hypothetical mechanism of action by the investigators.[32] In humans, UC-II reduces immune-mediated damage to joint cartilage, thereby improving joint mobility and flexibility in rheumatoid arthritis.[57] There are indications that the amino acids in GH stimulate the synthesis of collagen in human cartilage.[58] Feeding of β G in pigs reduces the plasma concentrations of the proinflammatory cytokines, IL-6 and TNFα and raised the concentration of the anti-inflammatory cytokine, IL-10.[59] MA affords good protection against adjuvant-induced arthritic states in rats.[60] The benefits of the anti-inflammatory properties of MSM in managing OA in humans has been investigated but could not be confirmed.[61] It is speculated that SMPC contains natural factors that inhibit inflammation by suppressing neutrophil emigration from the vascular space, possibly by restricting extravasation through tight junctions.[62] However, according to our criteria in this review, the global level of evidence of efficacy to alleviate clinical signs of OA was low for UC-II, β G, MA, MSM, SPMC, and AOV. HCA was ineffective in dogs.

This review also showed the limited numbers of rigorous randomized controlled trials and of participants in clinical studies. Among publications identified in databases, only controlled trials were considered as these constitute the highest level of evidence, which can be used for a question concerning therapeutics.[12,13,20] Only 22 studies were identified and, owing to this low number, the evaluation of consistency (step 4) between observations was rarely applicable. This lack of information may be because of different factors. (1) The veterinary pharmaceutical market represents only a small proportion of the pharmaceutical industry and it is unrealistic that research comparable to human medicine will be conducted in the veterinary field frequently.[63] (2) Nutraceuticals are not considered as medicinal products. Manufacturers do not have to provide scientific information to legal authorities. They tend to conduct and publish a scientific study to justify and support the use of their product to the consumers. However, they do not necessarily have an interest in repeating such studies, as these might result in negative findings. (3) It might also be difficult for investigators to publish a study that is similar to a previous one, but that addresses some shortcomings. Peer-reviewed journals might not prioritize publication of confirmatory studies.

To evaluate the methodological quality of studies, we built a new tool consisting in a set of questions (Table 1). It was consistent with different sources of recommendations about reporting in research.[20,25,64–67] Some elements of those recommendations were rarely considered in the publications about nutraceuticals, such as the description of randomization, allocation concealment, sequence allocation, blinding, flux of participants, periods of recruitment and follow-up, and baseline data. On the other hand, background, objectives, interventions, statistical results, and results were usually well reported. In Table 1, the weighting of items, though obtained via a Delphi process, reflects these authors' opinions and requires criticism and further validation. It might be argued also that the

CONSORT statement provides guidelines about how to report randomized controlled trials and not directly how it should be conducted. As a consequence, Table 1 would mix items that refer to the format of the manuscript (eg, how the background is adequately described in the introduction) with items that refer to the quality of the methodology (eg, how participants were blinded). However, the evaluation of the quality of the scientific information is performed via the manuscript that is available. In other words, investigators, in systematic reviews, do not often have the opportunity to check the raw data and the actual application of the methodology that is reported. Therefore, systematic reviews will remain limited to investigate published manuscripts, until a general consensus is reached by the scientific community about how to ensure transparency about data. This effort should be made at every level. For example, we suggest that our system of evaluation in this review, and the way results are reported (Table S1 in addendum), might provide transparency by providing the raw data (the references of the publications included in the review), the outcome measures (the question items), and the scores for every item, thus allowing readers to repeat the review and compare their personal rating to ours. We also suggest that Table 1 might be a useful educating tool for veterinary practitioners who are less aware of clinical epidemiology and critical review of publications. In veterinary medicine, other authors recommend developing strategies to facilitate the practice of EBM[17] and have shown that critical reviewing helps better understand EBM concepts.[68]

Several methodological weaknesses in the methodology of trials were identified (Table 1). First, objective outcome measures were rarely used. Lameness is traditionally evaluated semiobjectively by clinicians. Promulgators of evidence-based research recommend the use of objective instruments to validate outcomes and provide a standardized means for clinical assessment of the efficacy of veterinary treatments,[64–67] like kinematics and force plates.[27,32,47] We attributed a higher score to studies by means of objective outcome measures than to those relying upon semiobjective ones (eg, clinical test performed by a veterinarian) and, especially, on subjective evaluations such as owner's opinion. Secondly, the difficulty in recruiting patients and the importance of considering the power of studies and sample size in veterinary research have been emphasized.[15] This review shows that a low number of individuals were studied. It might be argued that criteria of quality were set too high and that, for example, we could have considered a moderate level of evidence when 1 or 2 high-quality studies demonstrated a significant effect with an adequate number of individuals in each group (eg, $n = 25$). Innes estimated that 25 dogs per group were an adequate sample size to detect a 10% difference in peak vertical force (measured with a force-plate) between the active treatment and placebo with a power of 80%.[27] We considered this sample size as the minimal requirement, although we are aware that power calculations vary with the expected magnitude in the difference in outcome between groups, the probability of the false-positive and false-negative conclusions one is willing to accept, and the nature of data.[69] Quantity of valuable information was also rarely adequate according to our criteria, that is, at least 3 studies assessing the same product. Although it was adequate for O3FA and GLM, it is to note that the 4 identified studies were performed by the same team of researchers for the former,[35–38] and 2 of the 4 studies we found came from the same team for the latter.[42,43] Thirdly, a statistically significant result does not indicate whether the observed effect has any clinical importance. The concept of "effect size," a unitless measure of the degree to which the apparent treatment effect exceeds the placebo effect, has not been widely reported in veterinary trials. Calculation and reporting of effect size in veterinary trials is a convenient construct for comparing the magnitude of outcomes within and among trials[4,70] and as such was considered in this review as an element of quality.[4] Fourthly, the discussion section is difficult to evaluate and may be biased by the interests of investigators, because several studies are sponsored or supported by manufacturers. We attempted to identify objective factors of quality of discussion such as whether authors were considering trial limitations, sources of potential bias, imprecision, applicability, other relevant evidence, benefits, and harm. The assessment of publications by 2 reviewers aimed to limit subjectivity.

There were also other methodological elements that influenced the evaluation of the efficacy of nutraceuticals, such as uncontrolled composition of the marketed product and combination of the nutraceuticals with others.

It must also be noted that the duration of treatment was variable and ranged from 90 to 180 days for O3FA, whereas shorter treatments (sometimes only 2 weeks[32]) were administered in other studies. Initial standardization is difficult as there will always be regimens (meaning dosage, treatment frequency, and treatment duration) that are not or less effective than others. Nevertheless, once a nutraceutical has been suggested to be effective in 1 group, conditions of administration should be defined if the purpose is to assess whether it is also effective in another group or to compare it with another product.

This systematic review demonstrates that the evidence of efficacy of nutraceuticals to improve pain or gait abnormalities in OA is poor, with the exception of diets supplemented with O3FA in dogs. This conclusion must be contrasted by the fact that, to date, systematic review remains an imperfect process. This article illustrates the limits of application of EBM in veterinary science with limited number of rigorous randomized controlled trials and of individuals in clinical trials. As a result of this veterinary context and the difficulty to design strong study designs, there is a risk that future systematic reviews about veterinary topics will continue to conclude that the level of evidence is not satisfactory. Although systematic reviews may also give the impression of a strong criticism by scientists

on the work of their colleagues, transparency and accountability policies are widely accepted strategies to drive quality improvement and stimulate consumer choice. It is important to work on the availability of informational tools at the disposal of practitioners, such as systematic reviews. It is also essential to request more clinical studies, and less confidentiality, about medicinal products and dietary supplements that are marketed, to better inform veterinarians. The culture of only publishing truly original research has also to change before we will be able to really practice EBM. It is necessary to continue the investigation about nutraceuticals in a standardized way to evaluate their potential role as disease modifier. In addition, guidelines should be elaborated to reach a standardization of systematic review of trials and observational studies to limit heterogeneity of results and ensure fair comparisons between studies. Their reporting would be improved by internationally agreed criteria for guidelines. Before all these changes have been implemented, we will have to remain very careful in our conclusions.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Detailed results of quality assessment of selected studies.

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