

THE ANTI-INFLAMMATORY EFFECTS OF TURMERIC IN LOCOMOTOR DISORDERS: A SHORT REVIEW

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Abstract

Pain and inflammation management in the medical field are necessary in every pathology regardless of the origin. When it comes to the veterinary field, pain and inflammation reduction is the key to full recovery, considering the animal patient's behavior in such cases. Also, because the medication may in some cases be inaccessible or hard to be administered, veterinarians and owners should take alternative medicine into account, as many literature researches had indicated high efficacy. This research aims to analyze the latest discoveries regarding the inflammation and pain management through curcumin treatment.

Keywords: musculoskeletal; pathology; alternative; medicine; curcumin; inflammation; pain.

INTRODUCTION

Ethno-veterinary practices research is a burgeoning area of inter-disciplinary research with enormous potential for learning many aspects of folk knowledge on domesticated animals. Medicinal plants and their therapeutic benefits in livestock care are attracting the attention of an increasing number of natural and social scientists, veterinary practitioners, livestock owners, and field workers in developing nations. The community-based local or indigenous knowledge and techniques of caring for, healing, and managing animals is a simple definition of ethno-veterinary medicine. This encompasses social practices as well as the integration of animals into systems. Ethno-veterinary medicine is the knowledge of local people about folk beliefs, skills, procedures, and practices related to animal health and production. Close observation of animals and/or oral transmission of experience from one generation to the next provide the foundation for this knowledge. Although it is or well nourished among pastoral nomads all over the world, most rural and tribal communities have this rich reservoir of local knowledge on practically all aspects of animals [Misra et al., 2004; Dejonckheere et al., 2016].

Curcumin is the yellow pigment found in turmeric (*Curcuma longa* L.), India's most popular spice and a key component of curry powders.

Turmeric has a rich history of medical usage, particularly for the treatment of inflammation, and many of its traditional uses have been mechanistically verified in cellular systems and animal disease models. Curcumin is one of the most researched botanical compounds in the biomedical literature, with about 3,000 preclinical studies. Curcumin acts as a master switch of inflammation, regulating pro-inflammatory enzymes (cyclooxygenases [COX] and lipoxygenases) as well as inflammatory transcription factors (nuclear factor-kappaB [NF-kB] and signal transducer and activator of transcription 3 [STAT3]) and their genomic expression, according to these studies. The majority of curcumin's therapeutic effects are suggested by epidemiological studies, corroborated by animal model studies, and extrapolated from in vitro studies, but not clinically validated [Misra et al., 2004; Clutterback et al., 2013].

Curcumin's poor stability, which is particularly unstable at gastrointestinal pH (half-life at pH 7 <10 min), and limited oral absorption contribute to this perplexing predicament. After oral administration of doses as high as 12 g/day, plasma concentrations of phase II metabolites (glucuronides and sulfates) hardly approach 50 ng/mL. Curcumin, once in the plasma, has a surprising stability and even permeability to hard-to-reach regions like the brain [Misra et al., 2004; Wynn et al., 2007].

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Like most dietary phenolics, curcumin is water and fat soluble in small amounts. It has polar groups (two phenolic hydroxyls and one enolic hydroxyl) that can engage with a complimentary group via hydrogen bonds and polar interactions, similar to phospholipid polar heads. Phenolics have a high affinity for biological membranes and, once complexed with phospholipids, are incorporated in a lipid matrix that protects them from hydrolytic degradation while allowing them to take advantage of the rapid exchange of phospholipids between biological membranes and extracellular fluids, which can lead to increased cellular uptake. These principles underpin the phytosome method for increasing phenolic bioavailability, and they have now been effectively applied to curcumin,^{5,6} a patented compound with phosphatidylcholine known as the Curcumin-phosphatidylcholine Complex [Misra et al., 2004].

This research assessed the long-term efficacy and safety of this curcumin in the management of different musculoskeletal pathologies, conditions in need of novel therapeutic options, based on very promising results in terms of improved hydrolytical stability, human pharmacokinetics, and previous clinical studies [Misra et al., 2004].

RESULTS

Turmeric has anti-inflammatory and antioxidant qualities, which help to eliminate free radicals, which are responsible for cell damage in the body. People who suffer from arthritis can benefit greatly from utilizing turmeric because of this feature and the same may be mentioned for the veterinary field [Verma et al., 2018].

[Caterino et al., 2021] has done a research upon the effect of turmeric in combination with boswellic acid in the treatment of osteoarthritis (OA) in dogs. There were twenty dogs included in the study (11 male, out of which only 1 neutered and 9 females, out of which 5 were neutered).

The dogs were separated into two groups at random: treatment (A) and control (B). Five dogs in the A group had elbow joint OA and five had stifle OA; four dogs in the B group had elbow joint OA and six had stifle OA. The mean body weight (BW) for groups A and B was 35.04 ± 4.89 kg and 35.36 ± 4.66 kg, respectively. In group A, the mean standard deviation OA grade was 2.3 ± 0.48 , while in group B, it was 2.2 ± 0.63 . There was no statistical difference in GFRs (glomerular filtration rates) or BW between the two groups at T0, indicating that the groups were homogeneous at that time [Caterino et al., 2021].

Because curcumin and boswellic acid are chemically distinct, their targets are likely to be distinct as well, therefore a combination of the two could explain their synergistic activity, which has been documented in both human and veterinary literature. The clinical significance of our findings implies that curcuma and boswellic acid have a key function in inflammation and pain alleviation, which is also supported by the literature [Caterino et al., 2021].

OA is a chronic degenerative disease for which there is no cure. The most typical treatment combines NSAIDs (Non-steroidal anti-inflammatory drugs) and nutraceuticals in a multimodal manner. Although, in veterinary medicine, the use of NSAIDs is limited due to long-term adverse effects. They treated dogs with a mild degree of OA exclusively with nutraceuticals administration for 90 days in this clinical research, with objectively satisfactory results observable after 60 days from the end of the treatment [Caterino et al., 2021].

Because forelimb PVF is generally higher than hind limbs, comparing gait analysis data from the thoracic and pelvic limbs in lame dogs may make data interpretation more complex. Data analysis at T0 revealed that the two groups were homogeneous in terms of OA localisation, score, GFRs, and BW, avoiding the need for rescaling, harmonization, or normalization, which is required in comparison research. Peak Vertical Force (PVF) and vertical impulse (VI) are two useful indices for assessing limb function. PVF is defined as the greatest force exerted perpendicular to the surface during the stance phase (ST), while VI is the computed area under the vertical force curve over time [Caterino et al., 2021].

As a result, in a lameness dog, a lower PVF indicates a lower bear weight and, as a result, a lower ST and VI. Despite the lack of statistical significance, we saw an improvement in PVF in 16/20 (80%) of patients in our clinical experiment, indicating that the nutraceutical can help with pain perception and hence lameness. Furthermore, the dogs given curcumin and boswellic acid had larger and more consistent overall PVF percent BW mean values until the study's end point than the control group [Caterino et al., 2021].

Furthermore, a statistically significant improvement in VI percent BW and ST in treated dogs over time indicates an improvement in limb function, demonstrating the therapeutic potential of curcuvet® and boswellic acid. The rising slope (RS) and falling slope (FS) of the force curve are defined as the time between the baseline value at ground initial contact and the maximal force, and the time between the maximal force and when

contact with the ground ceases, respectively. Because of the careful initial bear load and a faster release of weight from the limb in lame dogs, the RS is lowered and the FS is enhanced. In this clinical research, it was discovered that the RS was steeper in treated dogs, indicating faster bear loading, whereas the FS was less steep, indicating slower weight offloading [Caterino et al., 2021].

[Dejonckheere, 2016] mentions in a review that curcumin's anti-inflammatory benefits have been tested in people and rats in the majority of large-scale clinical trials. There are a couple of large horse and dog trials. A randomized, double-blind, placebo-controlled parallel group research using turmeric extract for the treatment of osteoarthritis in dogs failed to produce statistically meaningful results. Curcumin reduced macrophage multiplication, substantially downregulated TNF, and activated fibrinolysis, according to a small study involving 12 osteoarthritic dogs. These promising results will need to be confirmed in larger studies.

The pharmacodynamics of liposomal curcumin intravenous injection in beagles has been examined, although there are no practical uses for the average pet owner. A study demonstrated that feeding a dietary supplement including curcumin and boswellia extract to thoroughbred horses reduced pro-inflammatory cytokine expression and thereby improved exercise adaption. Large-scale investigations are required to confirm these conclusions once again. A study conducted at the University of Udine in Italy found that giving a phytosome complex of curcumin to seven mares with verified osteoarthritis and five foals with osteochondrosis alterations for fifteen days had some positive benefits. Gene expression was measured before, during, and after the treatment for four, eight, and fifteen days [Dejonckheere, 2016].

Even while only the downregulation of IL-1 and IL1RN was significant, curcumin suppressed the expression of COX-2, TNF-, IL-1, IL1RN, and IL6 in mares. Curcumin decreased COX-2, TNF-, and IL1RN expression in foals while significantly increasing IL6 expression [Dejonckheere, 2016].

These findings suggest that curcumin has potential, but this is a limited study. Curcumin at doses less than 25µM has a substantial antiinflammatory impact on cartilage explants in vitro, according to [Clutterbuck et al., 2013] [Dejonckheere, 2016].

The researchers cautioned against extrapolating the findings and suggested more research to determine curcumin's bioavailability and physiologically appropriate serum and

synovial concentrations in people and animals [Dejonckheere, 2016].

[Kobatake et al., 2021] also conducted a study on 40 dogs with degenerative myelopathy (DM). There were 26 male dogs, 21 of whom had been castrated, and 14 female dogs, nine of whom had been spayed. The average age of onset was 10 years and 8 months (range: 7 years and 7 months to 14 years old). The median age at death was 13 years and nine months (range: 10 years and three months to 16 years and one month), with a median surviving time of 36 months (from symptom onset to death) (range: 18 to 52 months). The c.118G>A mutation in the SOD1 gene was found in all of the dogs [Kobatake et al., 2021].

All of the cases began with spastic upper motor neuron (UMN) paresis and later proceeded to flaccid tetraplegia due to increasing widespread proprioceptive ataxia of the pelvic limbs. Thirty-one dogs had urinary incontinence, with 17 of them also having fecal incontinence. Urinary incontinence was found concurrently or after the beginning of fecal incontinence. Eleven dogs had dysphonia, particularly hoarseness, however the start of symptoms varied greatly between them. Three of the four dogs with dysphagia died within two months of the onset of dysphagia, while the fourth dog lived for seven months following the onset of dysphagia. Five dogs developed tongue spasms. The sense of the face in one dog deteriorated, indicating trigeminal nerve paralysis. Another dog suffered facial nerve paralysis, which meant he couldn't move its face. Patients that lived longer than the median survival period developed tongue spasms as well as facial and trigeminal nerve paralysis. The study also shows the occurrence and development of symptoms other than gait disturbance [Kobatake et al., 2021].

A large number of the dogs examined had dyspnea (34 of 40 dogs; 85.0%). The median time from the onset of dyspnea to death was 1.5 months (range: 0–22 months), with 11 of the 34 dogs dying within one month of beginning. Meanwhile, after the onset of dyspnea, five of the 34 individuals lived for more than a year. The correlation coefficient between the beginning of dyspnea and survival time was 0.76 ($p < 0.0001$), indicating a link between respiratory impairment and death. Symptomatic treatment, such as oxygen inhalation, was given in these patients when their usual veterinarian felt it necessary [Kobatake et al., 2021].

All of the incidents began with increasing pelvic limb paresis, which proceeded to flaccid tetraplegia. These findings imply a link between the start of dyspnea and survival time ($R = 0.72$, $p < 0.0001$) [Kobatake et al., 2021].

It was discovered that dogs with DM who were given curcumin had a considerably higher survival period than those who were not. Curcumin is a physiologically active polyphenolic molecule with a variety of effects on the central nervous system, including neuroprotective and anti-inflammatory properties. Furthermore, a prior study found that curcumin molecules bind tightly to the aggregation-prone areas of mutant SOD1 proteins and block the exposed aggregation site, preventing the development of unstructured SOD1 aggregates. Curcumin also has three documented favorable effects on muscles: (1) it promotes protein synthesis, (2) it reduces muscle protein breakdown, and (3) it reduces exercise-induced muscle damage. In the curcumin and control groups, there were no statistically significant changes in the time from onset to thoracic limb paresis. Nonetheless, in the curcumin group, the time from onset to nonweight bearing of the hind/thoracic limbs was greater. This shows that curcumin could help dogs with diabetes prevent neurodegeneration and muscular atrophy. Despite the uncertain benefit of curcumin in DM, dog owners who choose to administer curcumin to their pets may be more engaged in conservative care, such as physical therapy. As a result, extended survival may be due to the dog owner's approach to care rather than curcumin's therapeutic effects. In addition to nerves and muscles, curcumin has anti-inflammatory and antioxidant properties in other organs. As a result, improvements in motor function may be attributable to curcumin's action on joints rather than the DM disease itself [Kobatake et al., 2021].

CONCLUSION

Curcumin's use in the treatment of joint inflammation is supported by a large amount of clinical observational and anecdotal evidence, as well as some encouraging in vitro and in vivo research. However, large-scale clinical trials in dogs, as well as clinical veterinary research, are urgently needed to find strategies to improve the bioavailability and clinical usefulness of supplemental curcumin in the treatment of musculoskeletal pathology. Curcumin's relative safety should allow it to be used as a supplement to treat osteoarthritis and other muscular and skeletal pathologies in the vast majority of patients. For dogs, the recommended dose ranges from 50 to 250 mg curcumin three times per day [Wynn et al., 2007]. The active ingredients of veterinary nutraceutical products may vary significantly due to a lack of uniformity in extraction techniques and

quality monitoring. More veterinary clinical trials with more bioavailable forms of curcumin, on the other hand, will provide more precise dosing guidelines and standardised products.

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