https://doi.org/10.61900/SPJVS.2023.04.23

THE MANAGEMENT OF ARTHRITIC PAIN IN DOGS– A REVIEW

Daniela NEAGU[1], Clarisse LEBLOND[1], Alexandra BIRIȘ[1], Răzvan CODEA[1] , Cristian POPOVICI[1], Alexandra MUREȘAN[1]

e-mail: daniela.neagu@usamvcluj.ro

Abstract

Osteoarthritis is a common condition in dogs, particularly affecting elderly individuals, and the chronic pain it causes significantly impacts the quality of life of affected dogs. First, we will focus on the joint, the physiopathology of osteoarthritis, and the mechanisms of arthritic pain production, and then discuss the existing treatments. There are numerous treatments available for managing this complex osteoarticular condition, but unconventional therapies are increasingly of interest to owners of canine species. Phytotherapy harnesses the healing properties of plants for treatment in a less toxic, more natural, and more cost-effective manner, offering a wide range of therapeutic options for animals. The objective of this review is to evaluate the present evidence backing treatments for canine osteoarthritis. This includes non-steroidal anti-inflammatory drugs, piprants, monoclonal antibodies, adjunctive analgesics, structure-modifying osteoarthritis drugs, phytotherapy, and regenerative therapies.

Key words: dogs, arthritic pain, treatment.

INTRODUCTION

Osteoarthritis (OA) is defined as a degenerative osteo-articular condition that can evolve acutely or chronically. It is characterized by a progressive and irreversible degeneration of diarthrodial synovial joints. This disease involves a complex pathophysiology with numerous mediators responsible for pain that affects the quality of life of the affected animal. In order to manage this pain, it is necessary to understand the mechanisms of osteoarthritis, those of chronic pain, and the various treatment modalities that exist.

Canine osteoarthritis (OA) is highly prevalent in dogs, affecting up to 75% of adult medium-size and large breeds (Craig L.E., Reed A., 2012). According to one corporate report, there has been a 66% increase in OA cases in dogs over the past decade (Ashenhurst S., 2019). However, a recent study conducted in primary care practices suggested a lower prevalence of OA, at 2.5%, with a median age of diagnosis at 10.5 years (Anderson K.L., *et al*.,2018). This indicates that canine patients may not be screened early enough, owners may not be recognizing clinical signs, and veterinarians should consider assessing dogs for OA at an earlier age and initiating treatment accordingly.

Osteoarthritis can be classified into two categories, depending on the process by which it develops.

The origin of primary osteoarthritis is unknown, although it appears that the genetic component is predominant in its development in large breed dogs. Its age of onset depends on the breed, averaging around 3.5 years in Rottweilers and 9.5 years in Poodles (Melle E., 2007). Primary osteoarthritis can be localized to the limbs or generalized.

Secondary osteoarthritis is the most common in dogs. It develops secondary to congenital or acquired osteo-articular conditions such as hip and elbow dysplasia, osteochondritis dissecans, or hip and patellar luxations. It can also be secondary to musculoskeletal disorders such as cruciate ligament rupture or sprains. The common factor in these conditions is joint instability leading to the development of osteoarthritis; they are termed "arthrogenic.

[1]Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, Cluj-Napoca, Romania

Risk factors

In human medicine, the reported risk factors in the development of osteoarthritis are numerous and are generally related to genetics, sex, age, obesity, history of joint trauma, or underlying diseases. In veterinary medicine, primary osteoarthritis can be idiopathic but may also be associated with predisposing factors such as obesity and age. As for secondary osteoarthritis, due to an underlying disease, it is the most common form of osteoarthritis in dogs. According to a study by Melle E. (2007) the major risk factor is genetics, particularly in breeds such as Chow Chow, Dalmatian, Samoyed, Labrador, Bernese Mountain Dog, and German Shepherd. Clinically, osteoarthritis is more common in medium and large breed dogs (Genevois J.P. *et al*., 2008).

Synthesis of mechanisms involved in osteoarthritis

Osteoarthritis results from self-aggravating processes stemming from an imbalance between anabolism and catabolism within the articular cartilage. With catabolism being predominant, it surpasses the cartilage's repair capacities. Moreover, the repair process is not qualitative; the proliferation of chondrocytes in response to degradation is abnormal, and the newly synthesized collagen is abnormal as well. This corrective synthesis is therefore insufficient and ineffective, leading to the loss of the cartilage's biomechanical properties.

As chondrocytes deplete and undergo necrosis, the cellular component diminishes, and the mechanical component takes over, causing a decrease in the quantity of proteoglycans and hyaluronic acid in the cartilaginous extracellular matrix. This leads to cartilage degradation and synovial inflammation, producing inflammatory substances that perpetuate this vicious cycle (Lorenz H., Richter W., 2006).

The pain and its mechanisms

Arthritic pain is a chronic and pathological pain that can vary in intensity. It has a very negative effect on the quality of life and well-being of the animal and intensifies as the disease progresses (Lamont L.A., *et al*., 2000). It can be maladaptive, meaning it is "neuropathic" pain resulting from damage or dysfunction of the nervous system, as opposed to adaptive pain which follows "a potentially harmful stimulus to the body". Maladaptive pain can become chronic if adaptive pain is not treated early and correctly (Signoret M. *et al*., 2022).

To understand the management of arthritic pain, it is first necessary to understand the mechanisms of pain production and persistence.

In the case of osteoarthritis, the nociceptive innervation of the synovial joints involves sensory fibers located in the accessory ligaments, subchondral bone, and synovium. It has been demonstrated that substance P causes peripheral nerve sensitization in response to painful joint movements (Witt K.L., Vilensky J.A., 2012). Immunohistochemical studies by Witonski D. and Wagrowska-Danilewicz M. (2004) have shown that inflammation plays a role in the increase of substance P-related fibers, thus contributing to the persistence of pain. Indeed, if the pain persists, the mechanisms of pain can change and become chronic, leading to hypersensitivity and amplification of pain, as is the case in osteoarthritis (Lamont L.A., *et al*., 2000).

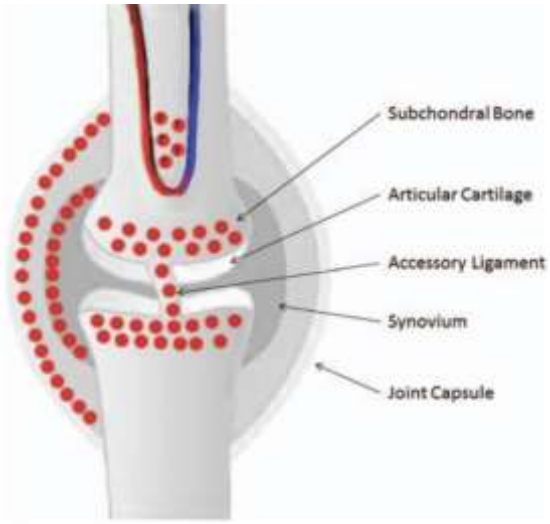

Figure 1. Diagram of the synovial joint. The red dots represent the location of nociceptors producing substance P, which is responsible for the pain message. The red dots with a question mark represent the location where pain may be of ischemic or vasospastic origin (Witt K.L., Vilensky J.A., 2012).

Inflammation plays a major role in the mechanism of arthritic pain, involving both its cellular and neurogenic components. Neurogenic inflammation results in an increase in the number of afferent fibers sensitive to substance P, which is widely distributed in the joint when it is affected. Thus, a vicious cycle is established; as inflammation increases, so does pain (Witonski D., Wagrowska-Danilewicz M., 2004).

Furthermore, according to Panizo M. (2019), the nerve growth factor (NGF) also plays a

role in the transmission of pain associated with osteoarthritis. In adulthood, in case of overexpression, this neurotrophin is produced by damaged tissues and inflammatory cells, then binds to receptors present on peripheral nerve endings. It thus activates the nociceptive signal and makes nerves more sensitive to painful stimuli. NGF also binds to receptors on inflammatory cells, which then secrete pro-inflammatory mediators, leading to additional NGF secretion. This creates a vicious circle of pain and inflammation (Panizo M., 2019).

There are various classes of analgesic medications with distinct mechanisms of action, each targeting nociception at different stages along the pain pathway. Therefore, it is crucial to adopt a multimodal approach to analgesia and management when treating canine osteoarthritis patients, particularly if there is an inadequate response to a single type of medication (Lascelles B.D.X. *et al.* 2008).

COMPONENTS OF MULTIMODAL MANAGEMENT OF ARTHRITIC PAIN

The goal of osteoarthritis treatment is to slow down the progression of the disease, reduce inflammation, and ultimately enhance the patient's quality of life.

Traditional management approaches for canine osteoarthritis typically encompass a range of strategies including: anti-inflammatory and analgesic medications, disease-modifying osteoarthritis agents, weight management, exercise modification, physical rehabilitation modalities, environmental modifications, surgical procedures. The majority of emerging therapies to treat moderate to severe pain are reformulations of existing analgesics combined with new delivery technologies, which may offer only incremental improvements in efficacy and safety. Currently, the greatest need in chronic pain treatment is to find treatments that do not have the drawbacks of NSAIDs and opioid analgesics (Fox S.M., 2016).

Managing osteoarthritis (OA) is a lifelong commitment aimed at reducing inflammation and slowing disease progression, while also enhancing muscle strength and endurance, maintaining joint range of motion, improving performance and function, and ultimately enhancing the quality of life (Millis D., 2021).

Medical Treatment

Surgical Treatment

Surgical treatment includes correcting the joint degradation process or arthrodesis of the already affected joint to eliminate pain. In many joint injuries, early surgical correction can prevent or slow down the development of arthritis. These interventions include procedures such as triple pelvic osteotomy, removal of abnormal cartilage in osteochondrosis, or joint stabilization. However, once the degenerative process has started, surgery cannot correct existing damage. In severe cases or those resistant to medical treatments, if feasible, arthrodesis involves fusing the bones of the joint and can help reduce pain (McLaughlin R., 2000).

Anti-inflammatories

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is the treatment of choice for reducing inflammation and arthritic pain. A wide variety of NSAIDs are available for use in animals, acting by reducing prostaglandin synthesis by inhibiting the enzyme COX. There are two types of COX; COX-2 is produced during cellular injury and generates prostaglandin synthesis, which leads to inflammation and pain (McLaughlin R., 2000).

Regarding the choice of the molecule, the efficacy of one NSAID over another varies little. Selective COX-2 inhibitors (such as carprofen or meloxicam) are preferred, and even COX-2 exclusive agents (such as true coxibs like firocoxib). Generally, the treatment duration is one week, but since arthritis is a progressive disease, long-term use is beneficial. If the molecule is well tolerated by the animal, it can be prescribed for four to six weeks and renewed as needed (Monteiro, B., Steagall, P.V., 2019).

The adverse effects that NSAIDs can cause include gastrointestinal irritation, nephrotoxicity, and coagulation problems (Signoret M. *et al*., 2022).

As for corticosteroids, their use in the treatment of osteoarthritis is controversial because they have long-term side effects and, at high doses, they inhibit the synthesis of collagen and proteoglycans. They can be used if osteoarthritis is resistant to other treatments or in case of NSAID intolerance, but always at a low dose to maintain their chondroprotective and anti-COX effects (Monteiro, B., Steagall, P.V., 2019).

Despite their widespread and obvious use in many cases, NSAIDs used alone are not always effective (Enomoto H. *et al*., 2018).

The renal effects of NSAIDs are also significant to consider. In cases of chronic kidney disease in dogs, there is an increase in COX-2 expression, leading to a shift in prostaglandin synthesis toward the COX-2 pathway. As a result, NSAIDs targeting COX-2 may potentially have adverse effects on renal function in dogs with chronic kidney disease (Lomas A.L. *et al*., 2015).

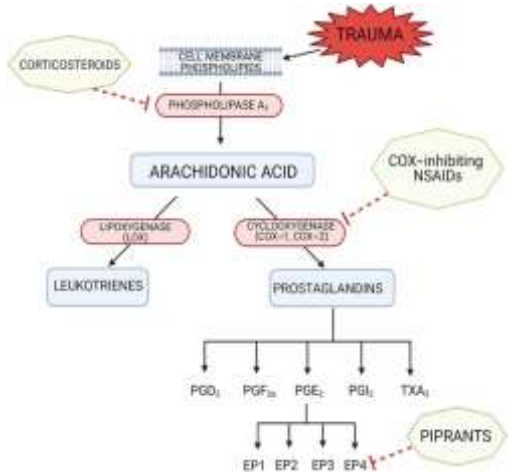

Figure 2-Targets of corticosteroids, COX-inhibiting NSAIDs, and piprants on the pathway of arachidonic acid metabolism are as follows (Monteiro and Steagall, 2019)

Monoclonal Antibodies

With a better understanding of the pathogenesis of osteoarthritis, immunomodulatory biological treatments have been introduced for the treatment of joint diseases. Unlike chemically synthesized drugs, they are derived from various natural sources (human, animal, microorganisms). Monoclonal antibodies are monovalent antibodies that specifically bind to target molecules such as cytokines, receptors, or cells, and block their activity (Enomoto H. *et al*., 2018).

Bedinvetmab and frunevetmab are monoclonal antibodies that bind to NGF and prevent its coupling with its receptor TrkA, thereby inhibiting the progression and amplification of the pain signal. According to the indications specified in the Summary of Product Characteristics (SPC), they should be used to relieve pain associated with osteoarthritis in dogs and cats, but there is no anti-inflammatory indication (Poitte T., 2023).

Adjuvants

Amantadine is an oral antagonist of the N-methyl-D-aspartate (NMDA) receptor, which may prove beneficial when administered alongside an NSAID. By blocking these receptors, it's possible to reduce central nervous system hyperresponsiveness, thereby enhancing the effectiveness of other analgesics. Amantadine can be administered continuously if necessary, although in some instances, it may be given daily for 7 to 14 days and then discontinued until pain exacerbates. Since elimination primarily occurs through the kidneys, dosage adjustments should be considered for cases of renal disease. While rare, potential side effects may include agitation or diarrhea (Lascelles B.D.X. *et al*., 2008). As adjuvants in a multimodal osteoarthritis protocol, amantadine can be used as an antagonist of NDMA receptors, which can be administered with gabapentin to modulate voltage-dependent calcium channels (Fox S.M., 2016).

Tramadol is a synthetic analogue of codeine widely used in veterinary medicine (although not approved in dogs), in addition to opioids or NSAIDs. In humans, tramadol is capable of reducing the amount of substance P and interleukin IL-6 in synovial fluid (Fox S.M., 2016).

Gabapentin is occasionally utilized as an adjunct pain medication for osteoarthritis (OA); however, its effectiveness for both acute and chronic pain management has been subject to questioning. (Wagner A.E. *et al*.,2010). Its most suitable application may lie in treating neuropathic pain. Pregabalin has also been employed for OA management. Potential side effects may include sedation and weight gain (KuKanich B., 2013).

Cannabinoids

Cannabinoids have been studied for several years and appear to be promising in the management of osteoarthritic pain. Dogs with osteoarthritis receiving high-CBD industrial hemp extract seem more comfortable and active. Further studies are needed to identify the long-term effects of CBD treatment, but short-term effects appear positive (Gamble L.J. *et al*., 2018). Pharmacokinetics, adverse effects, and drug interactions are yet to be determined. The doses used are low, as CBD does not have marketing authorization (Signoret M. *et al*., 2022).

Nutritional supplements

Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been linked to beneficial effects on osteoarthritis (OA). Studies have shown that they can increase weight-bearing capacity and reduce the dosage of NSAIDs required to maintain comfort in affected dogs (Johnson K.L. *et al*., 2020). Moreover, omega-3 fatty acids are known to decrease the levels of prostaglandin E2 in cartilage. They also compete with arachidonic acid in the cyclooxygenase (COX) and lipoxygenase pathways, leading to lower levels of inflammatory leukotrienes. Recommended doses for EPA and DHA range from 230 to 370 mg per kilogram of lean body weight(0.75) (Bauer J.E., 2011). A study investigating a veterinary therapeutic diet rich in omega-3 fatty acids administered to dogs with osteoarthritis (OA) revealed significantly higher peak vertical forces after 13 weeks compared to baseline measurements and compared to dogs fed a control diet (Moreau M. *et al*., 2013).

Glucosamine and chondroitin are frequently utilized in the management of osteoarthritis, although there is limited data available regarding appropriate dosage and efficacy (Bhathal A. *et al*., 2017). A recent study suggested that administration of glucosamine and chondroitin for 70 days led to improvements in subjective pain scores, weight-bearing, and overall condition compared to baseline values (Millis D. , Levine D., 2014) However, other studies have demonstrated minimal or no discernible effect (McCarthy G. *et al*., 2007).

Polysulfated glycosaminoglycans (PSGAGs) represent a class of disease-modifying osteoarthritis drugs known for their anti-inflammatory properties. They work by inhibiting matrix metalloproteinases within the joint and promoting hyaluronic acid (HA) and glycosaminoglycan synthesis in diseased joints. PSGAGs offer several beneficial mechanisms and are generally effective in alleviating lameness. However, it's important to note that they must be administered via injection (Fujiki M. *et al*., 2007).

Intra-articular Treatments

Hyaluronic acid (HA), platelet-rich plasma (PRP), mesenchymal stem cells (MSC), and corticosteroids are potential options for intra-articular therapies in osteoarthritis (OA).

Recently, mesenchymal stem cell (MSC) therapy for dogs with OA has been reviewed. Five studies have demonstrated improvements in pain, range of motion, and visual analogue scale scores in dogs treated with adipose-derived MSC, MSC plus PRP, MSC plus HA, or stromal vascular fraction. Additionally, one study suggested better outcomes with MSC compared to PRP six months after treatment. These improvements were observed to persist for a duration of 3 to 6 months. (Hoffman A.M., Dow S.W., 2016). Dogs treated with platelet-rich plasma (PRP) and hyaluronic acid (HA) exhibited significant improvement, with functional evaluation and impairments due to osteoarthritis (OA) showing enhancements ranging from 57% to 81%. Additionally, other studies have provided further support for the effectiveness of PRP in the treatment of OA (Vilar J. *et al*., 2018).

Phytotherapy

Phytotherapy is the field in which the active principles of plants are used for therapeutic purposes. Plants can be used in the form of Standardized Plant Extracts (SPE), essential oils, powders, crushed plant parts, or buds. Just like with allopathic molecules, the mechanism of action of active principles varies depending on the chosen plants (Wynn S.J., Fougère B., 2006).

The selection of plants was based on the individual properties of their active ingredients and their complementarity when combined, in order to achieve the desired effects in the treatment of arthritic pain. However, four plants of interest are commonly chosen, with one that may not be used in all dogs if they do not demonstrate the need for it: the blackcurrant (*Ribes nigrum L.*), the turmeric (*Curcuma longa L.*), the horsetail (*Equisetum arvense L.*) and the figwort (*Scrophularia nodosa L.*).

The blackcurrant *(Ribes nigrum L.)* can be used to treat several conditions thanks to its powerful anti-inflammatory action and is particularly recommended for animals suffering from painful joint disorders and has the advantage of being used for long-term treatments without triggering notable side effects. The proportion of Blackcurrant SPE is higher because it has a dose-dependent anti-inflammatory action. The active ingredients in blackcurrant leaf extracts are therefore excellent choices in the treatment of arthritic pain through phytotherapy: flavonoids, proanthocyanidols and phenolic acids.

Flavonoids possess significant anti-inflammatory properties, thanks to various mechanisms such as the inhibition of certain enzymes and transcription factors. They have the potential to inhibit enzymes involved in the metabolism of arachidonic acid like COX enzymes, thus inhibiting the biosynthesis of prostaglandins which play a crucial role in inflammation. Flavonoids can also modulate protein kinases by inhibiting transcription factors, such as NF-κB, which regulates several cytokines, chemokines, and cell adhesion molecules involved in inflammation (Malek S.J. *et al*., 2019).

Quercetin, one of the flavonoids present in the composition, is an exception as it is involved in reducing pro-inflammatory mediators. According to a study by Mamani-Matsuda M. *et al*. (2006), quercetin possesses anti-arthritic properties because it reduces the production of NO and TNF-α by macrophages. These mediators are involved in the inflammatory process and the transmission of pain signals.

Phenolic compounds exhibit anti-inflammatory action by inhibiting cPLA2α, which is cytosolic phospholipase A2. cPLA2α is an enzyme involved in COX synthesis, so it could be interesting to further inhibit this cascade upstream (Arnold J.B., 2016).

No toxicity has been reported currently. No drug interactions are known to date. It is mentioned a risk of laminitis in dogs with heart disease and a contraindication in case of edema

related to renal or cardiac insufficiency (Corbee R.J., 2022).

Frequent associations: In case of joint inflammation, it would be interesting to combine blackcurrant with meadowsweet (*Filipendula ulmaria*) and horsetail (*Equisetum arvense*), which are also plants with anti-inflammatory properties at the osteoarticular level (Wynn S.G., Fougère B., 2006).

The standardized extract of Turmeric *(Curcuma longa L.)* is a herbaceous plant native to Asia, is primarily indicated as an anti-inflammatory and chondroprotective agent. It is also recommended for dyspepsia with hepatic or biliary disorders, pancreatitis, or cancer. Of particular interest here is its indication for all chronic or acute inflammations such as arthritis and osteoarthritis. Additionally, it is also considered a good analgesic, which represents an additional beneficial property in the treatment of osteoarthritic pain. The dose of curcumin contained in the Standardized Plant Extract should be 3 mg/mL to achieve significant efficacy.

Curcuminoids exert anti-inflammatory and chondroprotective effects, with curcumin being the primary active compound responsible for these actions. Its mechanisms of action are diverse and multifaceted. According to a study by Shakibaei *et al.* (2007) conducted on osteoarthritis in humans, curcumin inhibits the degradation of kinases activated by IL-1β, which are responsible for the activation of the transcription factor NFkB. Consequently, curcumin prevents the translocation of NF-kB into the nucleus, thereby inhibiting its transcriptional activity. NF-kB regulates numerous pro-inflammatory genes, including MMP and COX-2, as well as signaling proteins like type II collagen and integrin β1 in chondrocytes. By inhibiting NF-kB activation, curcumin prevents the cyto-kinetic activation of pro-inflammatory enzymes in chondrocytes (Corbee R.J., 2022).

It allows the inhibition of prostaglandins and enzymes involved in inflammatory joint conditions such as tyrosine and hyaluronidase. Moreover, it also acts on phospholipases, lipoxygenases, thromboxanes, collagenases, IL-2 and IL-6, TNF-α, and NO production. These numerous sites of action enable it to act on the inflammatory cascade, and according to a study, its effect would be comparable to that of ibuprofen prescribed for knee arthritis. (Corbee R.J., 2022).

The abundance of curcuminoids in turmeric makes it an excellent choice for use in anti-inflammatory therapeutic preparations to treat osteoarthritis. Turmeric appears to be the quintessential anti-inflammatory plant, so its inclusion in the protocol seemed indispensable to me.

No toxicity has been reported currently. No drug interactions are known to date. An eventual contraindication might be the presence of gallbladder obstruction in the patient . However, this seems to be more commonly encountered in human medicine (Pandey N. *et al*., 2011).

Frequent associations: In cases of arthritis, it would be interesting to combine turmeric with meadowsweet (*Filipendula ulmaria*) and figwort (*Scrophularia nodosa*), which are also plants with anti-inflammatory properties at the osteoarticular level. In my choice of phytotherapeutic preparation, I have indeed decided to select figwort (*Scrophularia nodosa*) for some dogs, as we will see in the subsequent description of the chosen plants.

The field horsetail *(Equisetum arvense L.)* should not be confused with marsh horsetail, which is toxic. It's a plant that doesn't have flowers. It has long been used as a remineralizing and diuretic plant (Pandey N. *et al*., 2011). Field horsetail can be used in various cases such as osteoarthritis, skin ulcerations, and dysfunctions of connective and bone tissue such as rickets or tracheal collapse. However, its most notable effect is its usefulness in healing bone lesions and connective tissues.

In a study by Johnson K.A. *et al.* (2020), it was concluded that field horsetail has a remarkable therapeutic effect on rheumatoid arthritis in humans, and its clinical application is safe and reliable. It has an inhibitory effect on the cellular factor TNF-α involved in osteoarthritis, meaning that field horsetail can regulate the level of the pro-inflammatory factor TNF-α as well as the level of the anti-inflammatory factor IL-10. This is one of the mechanisms of action of field horsetail in the treatment of osteoarthritis. We will further explore these properties in the study of the active principles of field horsetail.

Field horsetail is the quintessential plant for silica. Silica, one of the most abundant mineral elements in terrestrial soils, mainly exists in the form of silicon dioxide (SiO2) or silicate (in clays). This is the role of field horsetail, which extracts mineral silicon from the soil, metabolizes it, and makes it available for assimilation by animals-organic silicon (Wynn S.G., Fougère B., 2006).

Organic silicon is involved in numerous physiological mechanisms of the body and is essential for the formation of cartilage in young bone; it is a component of glycosaminoglycans, which are constituents of the extracellular matrix of the joint. The importance of silicon has been demonstrated by studies on cell cultures of chondrocytes or osteoblasts; in environments

supplemented with organic silica, these cells showed higher growth rates. Indeed, in a silica-rich environment, the enzyme prolyl-hydroxylase, used as a marker for collagen synthesis, reaches its maximum activity. Indeed, the significant silica content of horsetail makes it an essential cartilage restructuring plant (Wynn S.G., Fougère B., 2006).

Horsetail contains flavonoids such as apigenin, luteolin, kaempferol, and quercetol. Flavonoids can also modulate protein kinases by acting on transcription factors like NF-κB, which regulates the expression of numerous inflammation-related molecules such as cytokines, chemokines, and cell adhesion molecules (Maleki S.J. *et al*., 2019).

Field horsetail has an anti-edematous action that proves to be interesting in rheumatology, particularly in acute arthritis. It's the saponins present in its composition that are responsible for this diuretic action. The important active principles in field horsetail are thus silicon and flavonoids, which make it a plant with significant reconstructive and anti-inflammatory properties.

No toxicity of field horsetail is known to date. Even though silica-rich plants appear contraindicated in cases of fibrosarcoma or osteosarcoma due to their potential for exacerbation, no contraindication in the use of field horsetail is known to date. However, some authors mention a contraindication to the use of field horsetail in cases of hypertension or heart disease. Field horsetail may potentially interact with the intake of cardiac glycosides, diuretics, or lithium.

To aid in the healing of bone lesions and connective tissues, horsetail tincture combines well with comfrey (*Symphytum officinale*) or nettle (*Urtica dioica*) and serves as an excellent complement to glucosamine and chondroitin sulfate supplements (Wynn S.G., Fougère B., 2006).

The scrophularia plant *(Scrophularia nodosa L)* is more precisely referred to as scrophularia nodosa because and is indicated for all inflammatory processes, especially at the osteoarticular level.

The anti-inflammatory effects of the scrophularia occur through complex and not fully elucidated mechanisms. However, the iridoids it contains intervene at the level of the NF-κB pathway, inhibiting the synthesis of TNF-α, IL-6, COX-2, and NO synthase. Consequently, the synthesis of inflammation-mediating prostaglandins is inhibited, and factors inducing the production of inflammation molecules are also inhibited. Iridoids thus enable scrophularia to be an anti-inflammatory and analgesic plant. According to Wynn S.G. and Fougère B., (2006), scrophularia is one of the ten essential plants in phytotherapy because it is the NSAID par excellence in phytotherapy.

No toxicity of field horsetail is known to date. Scrophularia is contraindicated in cases of gastric ulcers, gestation, and heart failure. Scrophularia may potentially interfere with the intake of cardiac glycosides (Wynn S.G., Fougère B, 2006).

Frequent associations: Scrophularia can be associated with Turmeric (*Curcuma longa*) and Ginkgo (*Ginkgo biloba*) in case of inflammatory flare-ups of arthritis on a background of osteoarthritis or with Horsetail (*Equisetum arvense*) and Nettle (*Urtica dioica*) in case of chronic osteoarthritis with structural loss (Wynn S.G., Fougère B, 2006).

For the treatment of arthritic pain, other plants mentioned in the literature could have been used, such as meadowsweet (*Spirea ulmaria*) and white willow (*Salix alba*), for example, which are known as "aspirin" plants and have a real interest in the pain relief treatment of painful joints (Corbee R.J., 2022).

Non-pharmacological treatment

Physical Exercise

Osteoarthritic pain makes the dog inactive, which promotes the worsening of the disease. Indeed, inactivity leads to muscle wasting and joint stiffness, which then intensify clinical signs. It is recommended to take the dog for a leash walk once a day or at least three times a week, outside periods of acute pain (Goldberg M.E., 2022).

Diet

Controlling the animal's weight is important. Overweight is a exacerbating factor for osteoarthritis; the constraints are stronger, which perpetuates inflammation and pain. Long-term treatment of arthritic dogs requires tailored nutrition.

There are foods containing EPA and essential omega-3 fatty acids that act against the enzymes responsible for cartilage degradation. This concept of "nutrigenomics" has shown good results in terms of pain reduction in dogs on this diet for several weeks. Furthermore, certain dietary supplements called "chondroprotective agents" exist, containing constituents of the cartilage matrix such as GAGs and hyaluronic acid. They do not prevent cartilage degradation but seem to slow down its progression. The benefit of their use can only be obtained after several months and at early stages of osteoarthritis (for example, with a one-

month course renewable four times a year) (Goldberg M.E., 2022).

Physiotherapy

In physiotherapy, it is important to determine the type of pain being addressed to employ appropriate techniques. Osteoarthritic pain is generally categorized as nociceptive pain. For this type of pain, commonly used techniques include transcutaneous electrical nerve stimulation (TENS), ultrasound therapy, laser therapy, and extracorporeal shockwave therapy. These methods have analgesic effects by releasing enkephalins and endorphins locally, which act on nerve endings originating the nerve impulses (Goldberg M.E., (2022).

According to Millis D. and Levine D. (2014), thermotherapy can be useful in pain management. Cryotherapy, which involves the use of cold, inhibits cartilage-degrading enzymes (proteases, hyaluronidase, collagenase) and minimizes the release of histamine, which is responsible for tissue damage. Vasoconstriction of blood vessels helps decrease pain by raising the activation threshold of nociceptors. It typically involves applying ice packs for ten to twenty minutes on the joint. As for heat therapy, the most significant beneficial effects include vasodilation, which allows tissue reoxygenation, denaturation of degradation proteins, and pain relief by inhibiting motor neurons. Hot packs or compresses are applied for fifteen to thirty minutes (Millis D., Levine D., 2014).

General physiotherapy techniques can also be used in addition; active exercises on a leash, on a treadmill, or in water, passive stretching, and massages to promote muscle strengthening, improvement of joint range of motion, and limb extension (Fox S.M., 2016).

Acupuncture

Acupuncture stimulates the meridians, which are "channels carrying vital energy to stimulate or inhibit the activity of certain regions of the body," using needles. The first analgesic effect relies on vasodilation; the release of bradykinin and increased local adenosine inhibit action potentials, resulting in an antinociceptive and anti-inflammatory effect. Additionally, the secretion of endorphins and endogenous opioids inhibits COX2 enzymes, thus reducing prostaglandin production. Acupuncture also promotes the synthesis of pain-modulating neuropeptides and inhibits the polarization of afferent fibers (Goldberg M.E., 2022).

Indeed, there are various alternative treatments for osteoarthritis (OA), including: chiropractic, therapy, massage therapy, pulsed electromagnetic field therapy, prolotherapy, joint mobilization and manipulation, radiation therapy, nuclear magnetic resonance treatment. Further research and development are needed before IL-10 plasmid DNA therapies become commercially available. However, this area shows promise for future advancements in the treatment of osteoarthritis (OA).

CONCLUSION

Arthritis is a complex and multifactorial condition requiring serious management, which can be done in a multimodal manner. Advancements in understanding the biology and pain mechanisms of osteoarthritis (OA) have resulted in an expanding array of pharmaceutical treatment options for canine OA over the past decade. The introduction of novel medications such as anti-nerve growth factor monoclonal antibodies (anti-NGF mAbs) and piprants, along with an increasing number of adjunctive analgesics and the wider availability of regenerative therapies in veterinary medicine, has provided veterinary practitioners with a broader range of therapeutics to offer, potentially enhancing the welfare of dogs with this condition. Phytotherapy appears to be an alternative of interest compared to conventional treatments; it is increasingly appealing to pet owners due to its accessibility, naturalness, and low toxicity. It can be used alone or as a complement, depending on the cases, and highlights the virtues of plants whose active principles all act in a complementary or potentiated manner to provide maximum efficacy. While these treatments may not be as extensively researched or widely accepted as conventional therapies, some individuals find relief from OA symptoms through these modalities. It's important for pet owners to consult with a veterinarian to determine the most appropriate treatment plan for their dog's specific condition.

REFERENCES

Anderson K.L, O'Neill D.G., Brodbelt D.C., et al., 2018 *-Prevalence, duration and risk factors for appendicular osteoarthritis in a UK dog population under primary veterinary care*, Sci. Rep.,8(1):5641.

Arnold J.B., 2016- *Lateral wedge insoles for people with medial knee osteoarthritis: one size fits all, some or none?,* Osteoarthritis and Cartilage, 24, (2), 193-195.

Ashenhurst S., 2019- *Osteoarthritis in pets on the rise alongside obesity epidemic, Veterinary Practice News*, available on-line at: https://www.veterinarypracticenews.ca/

Bauer J.E., 2011- *Therapeutic use of fish oils in companion animals*, JAVMA, 239(11):1441-1451.

Bhathal A., Spryszak M., Louizos C., Frankel G., 2017 *-Glucosamine and chondroitin use in canines for osteoarthritis: a review*, Open Vet J.,7(1):36-49.

Craig L.E., Reed A., 2012- *Age-associated cartilage degeneration of the canine humeral head*, Vet Pathol., 50(2):264-268.

Corbee RJ., 2022- *The efficacy of a nutritional supplement containing green-lipped mussel, curcumin and blackcurrant leaf extract in dogs and cats with osteoarthritis*, Veterinary Medicine and Science, 8(3):1025-1035.

Enomoto H., Fujikoshi Sh., TsujiT., Sasaki N., Tokuoka H., Uchio Y., 2018- *Efficacy of duloxetine by prior NSAID use in the treatment of chronic osteoarthritis knee pain: A post hoc subgroup analysis of a randomized, placebo-controlled, phase 3 study in Japan*, Journal of Orthopaedic Science, 23(6):1019-1026.

Fox S.M., 2016- *Multimodal Management of Canine Osteoarthritis*, CRC Press, Manson Publishing, London, 43-91

Fujiki M., Shineha J., Yamanokuchi K., et al., 2007- *Effects of treatment with polysulfated glycosaminoglycan on serum cartilage oligomeric matrix protein and C-reactive protein concentrations, serum matrix metalloproteinase-2 and -9 activities, and lameness in dogs with osteoarthritis*, Am. .J Ve.t Res.., 68(8):827-833.

Gamble L.J., Boesch J.M., Frye Ch.W., Schwark W.S., Mann S., Wolfe L., Brown H., Berthelsen E.S., Wakshlag J.J., 2018- *Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs*, Front. Vet. Sci., Sec. Veterinary Surgery, 5:165

Genevois J.P., Remy D. , Viguier E. , Carozzo C., Collard F., Cachon T., Maitre P., Fau D., 2008- *Prevalence of hip dysplasia according to official radiographic screening, among 31 breeds of dogs in France-A retrospective study*, Vet. Comp. Orthop. Traumatol., 21(01): 21-24.

Goldberg M.E., 2022, *Osteoarthritis in canines part 2: physical rehabilitation*, The Veterinary Nurse, 13(1):10.

Hoffman A.M., Dow S.W., 2016- *Concise review: stem cell trials using companion animal disease models,* Stem Cells., 34(7):1709-1729.

Johnson K.A., Lee A.H., Swanson K.S., 2020- *Nutrition and nutraceuticals in the changing management of osteoarthritis for dogs and cats*, JAVMA, 256(12):1335-1341.

KuKanich B., 2013- *Outpatient oral analgesics in dogs and cats beyond nonsteroidal antiinflammatory drugs: an evidence-based approach*, Vet. Clin. Small. Anim. Pract., 43(5):1109-1125.

Lamont L.A., Tranquilli W.J., Grimm K.A.,2000- *Physiology of Pain*, Veterinary Clinics : Small Animal Practice, 30(4): 703-728.

Lascelles B.D.X., Gaynor J.S., Smith E.S., et al., 2008- *Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs*, J. Vet. Intern. Med., 22:53-59.

Lorenz H., Richter W., 2006- *Osteoarthritis: Cellular and molecular changes in degenerating cartilage*, Progress in Histochemistry and Cytochemistry, 40(3): 135-163.

Lomas A.L., Grauer G.F., 2015- *The renal effects of NSAIDs in dogs*, JAAHA, 51(3):197-203.

Maleki S.J., Crespo J.F., Cabanillas B., 2019- *Anti-inflammatory effects of flavonoids*, Food Chemistry, 299:125-124.

Mamani-Matsuda M., Kauss T., Al-Kharrat A., Rambert J., Fawaz F., Thiolat D., Moynet D., Coves S., Malvy D., Djavad Mossalayi M.D., 2006- *Therapeutic and preventive properties of quercetin in experimental arthritis correlate with decreased macrophage inflammatory mediators*, Biochemical Pharmacology, 72(10):1304-1310.

McCarthy G., O'Donovan J., Jones B., et al., 2007- *Randomised double-blind, positive-controlled trial to assess the efficacy of glucosamine/chondroitin sulfate for the treatment of dogs with osteoarthritis*, Vet J.,174(1):54-61.

McLaughlin R., 2000- *Management of Chronic Osteoarthritic Pain,* Veterinary Clinics : Small Animal Practice , 30(4): 933-949,

Melle E., 2007- *Epidemiology of Osteoarthritis,* Veterinary Focus, 17(3):89-99.

Millis D., Levine D., 2014- *Canine Rehabilitation and Physical Therapy*, Saunders W.B., Elsevier Health Sciences, 254-277

Millis D., 2021- *Multimodal pain management for canine osteoarthritis*,Today's Veterinary Practice, 11(5): 43-49.

Monteiro, B., Steagall, P.V., 2019- *Antiinflammatory drugs*, Veterinary Clinics of North America: Small Animal Practice, 49, 993-1011

Moreau M., Troncy E., del Castillo J.R., et al., 2013- *Effects of feeding a high omega-3 fatty acids diet in dogs with naturally occurring osteoarthritis*, J. Anim. Physiol. Anim. Nutr. (Berl.),97(5):830-837.

Panizo M., 2019- *Les maladies congénitales orthopédiques chez le chat*, La Semaine Vétérinaire, 1804

Pandey N., Rai S.K., Rai S.P., 2011- *Medicinal plants derived nutraceuticals: a re-emerging health aid*, Int. J.Pharm. Bio. Sci., 2(4): 419-441.

Poitte T., 2023- *Trattamento del dolore osteoartritico cronico con anticorpi monoclonali: osservazioni cliniche*, Summa Animali da Compagnia, 2023, 40(1): 35.

Sellam J., Berenbaum F., 2010- *The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis*, Nature Reviews Rheumatology, 6: 625–635.

Shakibaei M., John T, Schulze-Tanzil G.,Ingo Lehmann I., Ali Mobasheri A., 2007- *Suppression of NF-κB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis*, Biochemical Pharmacology, 73(9): 1434-1445.

Signoret M., Gros L., Dumont R., Dally C., Le Boedec K., Cauzinille L., 2022- *Spinal epidural and synovial lipomatosis in a 3-year-old Eurasian dog receiving sustained steroid therapy*, Veterinary Medicine and Science, 8(4): 1339-1849.

Vilar J., Manera M., Santana A., et al., 2018- *Effect of leukocyte-reduced platelet-rich plasma on osteoarthritis caused by cranial cruciate*, in: Gait analysis of the effect of PRP in dogs with CCLR, PLOS ONE, 1-12.

Wagner A.E., Mich P.M., Uhrig S.R., Hellyer P.W., 2010- *Clinical evaluation of perioperative administration of gabapentin as an adjunct for postoperative analgesia in dogs undergoing amputation of a forelimb*, JAVMA, 236(7):751-756.

Witoński D., Wągrowska-Danilewicz M., 2004-