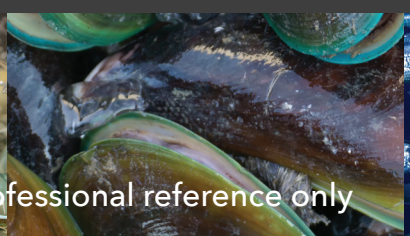
paw
Pure Animal Wellbeing
By BLACKMORES

JOINT CARE

Osteoarthritis in dogs & cats

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Did you know?

80% of dogs **over 8 years** of age suffer from **osteoarthritis?**[1]

What is Osteoarthritis?

The average age of companion animals has risen by 70% since the 1930s, and as a result veterinarians are spending more time caring for senior patients.[2] Senior patients are often affected by degenerative joint disease (DJD), which has been identified as one of the most significant and under-diagnosed diseases of cats and dogs.[3] In dogs over 8 years of age, 80% have osteoarthritis (OA), and even within younger populations of patients, it is suggested that 20% of dogs over one year of age are affected by progressive changes of osteoarthritis, whether through conformational abnormalities, genetic predisposition or injury.[1, 4]

Osteoarthritis is a progressive and chronic condition affecting the joints that can be characterised by pain, lameness and loss of function. It is associated with pathological changes in the tissue of synovial joints such as the loss of cartilage.[4] Currently, no cure exists, and treatment is limited to condition and symptom management.[5]

Pathophysiology and symptoms of osteoarthritis

OA is considered a multifactorial condition with a strong genetic component, and is impacted by lifestyle choices, diet, and type/amount of exercises. OA typically results from joint instability due to ligament laxity, injury or congenital abnormalities in bone/cartilage development.[6] It is commonly thought of as a disease of aging, as most cases are not diagnosed until a pet reaches senior years. However, OA can in fact begin at any age, and degeneration may already be present before OA is diagnosed.[7]

Morphological changes observed in OA include cartilage erosion and synovial inflammation (synovitis). Activated synoviocytes and chondrocytes release inflammatory cytokines which upregulate genes involved in cartilage degradation. These cytokines also blunt the innate ability for chondrocytes to restore the cartilage extra cellular matrix, leading to further catabolism.[8]

Osteoarthritis affects pets inside & out

On the inside[9]

Cross section of healthy joint (left) and arthritic joint (right)

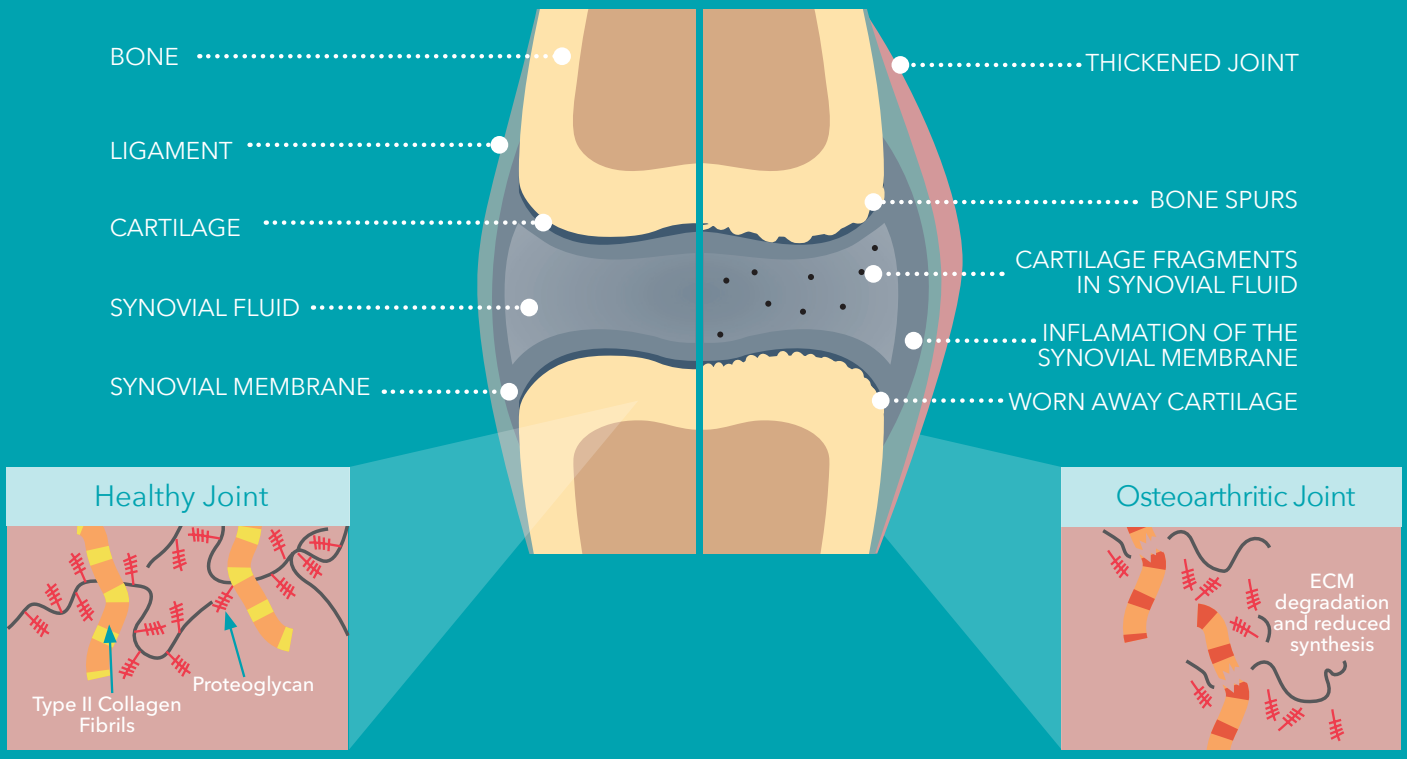
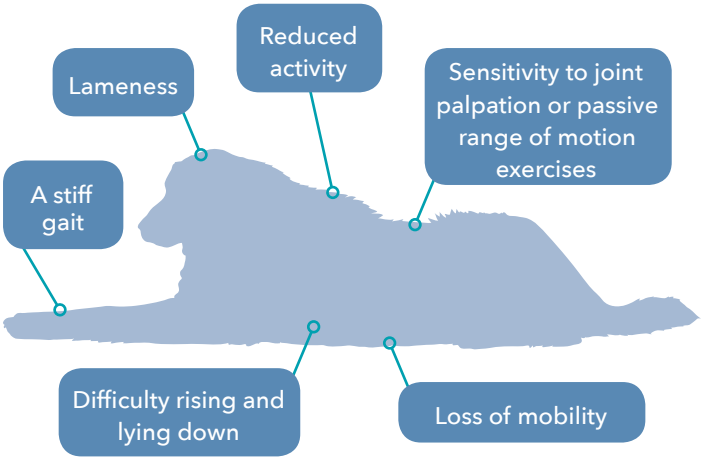


Image 1 shows the cross section of a healthy and arthritic joint and the physical changes that occur during joint degradation

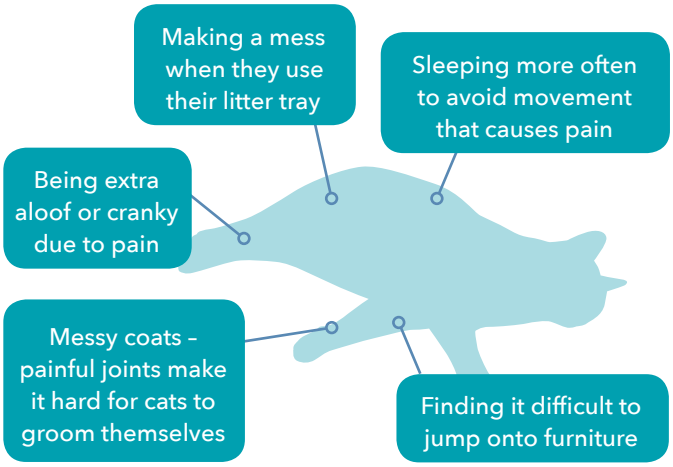
On the outside

Whilst early changes are not readily apparent, as the pathology progresses and involves more of the synovial membrane and subchondral bone, this is when the pain sensation usually begins to arise.

The first signs of OA in dogs that may be visible to an owner or clinician may include:[6]



Cat's symptoms are often more subtle and commonly not associated by owners as signs of pain or OA. They may include:



The pathophysiology of osteoarthritis[10]

Both inflammatory and immune processes impact the development and progression of osteoarthritis. These processes perpetuate each other, increasing the complexity of management of OA.

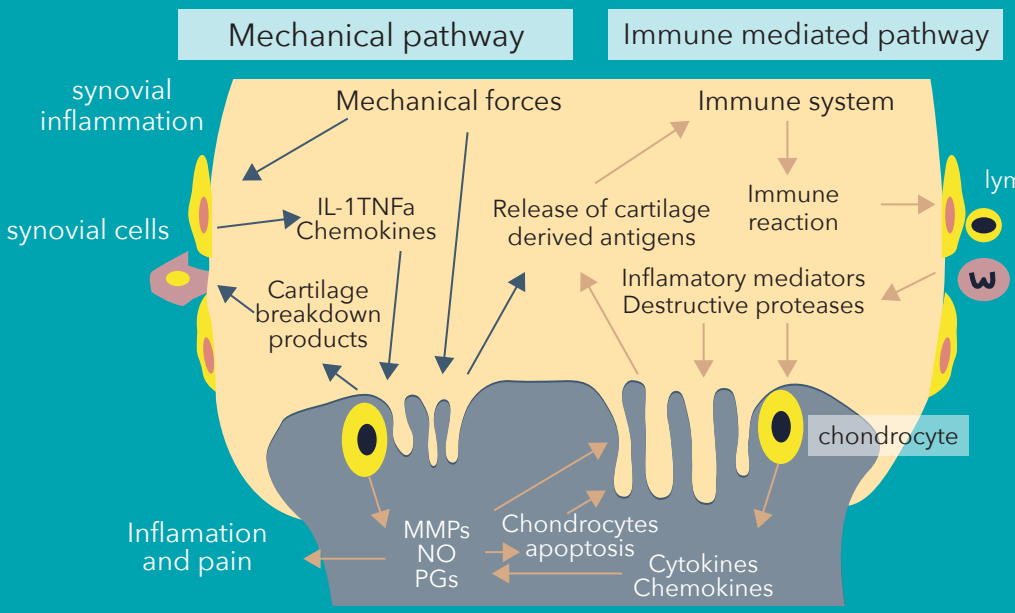


Image 2 is lifted from Yuan G., Et al. *Immunologic Intervention in the Pathogenesis of Osteoarthritis*. (2003) and shows the interaction between the inflammatory and immune pathways involved during osteoarthritic cartilage degradation

Understanding the abbreviations associated with osteoarthritis

ABBREVIATION	NAME	ACTION
ECM	Extracellular matrix	Comprised primarily of collagen & proteoglycans
PGE2	Prostaglandin 2	↑ Pain & swelling[3] ↑ Inflammatory tissue injury[3]
LT	Leukotriene	↑ Inflammatory cytokine, IL-1 & TNF-α[3] ↑ Activation of T Cells & macrophages (leading to ↑ ROS)[3]
AA	Arachadonic acid	EFA which is a precursor to leukotrienes, prostaglandins & thromboxanes
LOX	Lipo-oxygenase	Enzyme pathway that converts arachidonate to Leukotrienes
COX	Cyclo-oxygenase	Enzyme pathway that converts arachidonate to Prostaglandins
MMP	Matrix metalloproteinase	Degrade ECM especially type II collagen [3,12] ↑ Cartilage destruction ↑ Inflammatory cytokines
IL-1, 6, 8, 10	Interleukin	Cytokines associated with inflammatory process and increasing pain & ECM degradation[11] IL-1, 6 & 10 ↑ MMP[12] IL – 1 & 6 ↑ ECM protein degradation ↑ Cartilage destruction
ROS	Reactive oxygen species	Includes NO (nitric oxide)[11] ↑ Cartilage degradation[11] Act as catabolic cell signalling molecules[11]
TNF-α	Tumour necrosis factor – alpha	Signalling protein involved in inflammation[12] ↑ PGE2, ↑ ROS, ↑ MMP, ↑ ECM protein degradation[12] ↑ Cartilage destruction[12]
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells	Activated by inflammatory cytokines[12] ↑ MMP[12] ↓ ECM synthesising molecules[12] ↓ Synthesis of Type II collagen & aggrecan[12]
iNOS	Inducible nitric oxide synthase	iNOS is the enzyme that synthesises NO It is activated by various inflammatory cytokines including TNF-α & IL-1[13]

Osteoarthritis multimodal management

1. MAINTAIN AN IDEAL BODYWEIGHT

Reduce mechanical load through the joints

Carrying excess bodyweight will aggravate existing osteoarthritis and can increase the risk of developing it. Maintaining an ideal bodyweight should form the foundation of every osteoarthritis management plan.

2. REGULAR, GENTLE EXERCISE

Mobilise joints & maintain muscle mass & strength

Low-impact activities such as gentle leash walking and swimming for dogs are preferable to activities that can aggravate inflammation within joints such as running, jumping and catching balls and sticks. Encourage cats to move around by letting them outside where possible, leash walking with a harness or playing gentle hunting/stalking games.

3. ENVIRONMENTAL MODIFICATION

Reduce joint stress & strain

Supportive, comfortable bedding, additional warmth in cooler weather, and covering slippery surfaces with carpets, rugs or non-slip mats can assist pets live in their home with ease. In addition, providing ramps or steps up to heights to reduce the impact of jumping can also help.

4. NUTRITIONAL SUPPLEMENTATION

Provide nutrients to support joint health and relieve symptoms

Choose high quality, standardized supplements containing ingredients such as glucosamine and chondroitin sulfate for supporting cartilage health. Fish oil, green lipped mussel and herbs such as curcumin and boswellia may reduce inflammation & relieve symptoms of osteoarthritis.

5. MEDICATE WHERE NECESSARY

NSAIDs & other medications may be required for advanced pain relief

Medications to reduce pain and inflammation are often a necessary component of a multimodal arthritis management plan, particularly in advanced cases. However, if osteoarthritis is being managed holistically, doses of these drugs and therefore their side effects, may be able to be reduced.

6. EMPLOY PHYSICAL THERAPIES

Acupuncture, physiotherapy, therapeutic laser, cold therapy and more

Many of these new approaches to managing osteoarthritis symptoms are becoming more widespread. Therapeutic exercise can be useful to maintain joint mobility and muscle strength where approriate and also has a valuable place in a multimodal management plan.

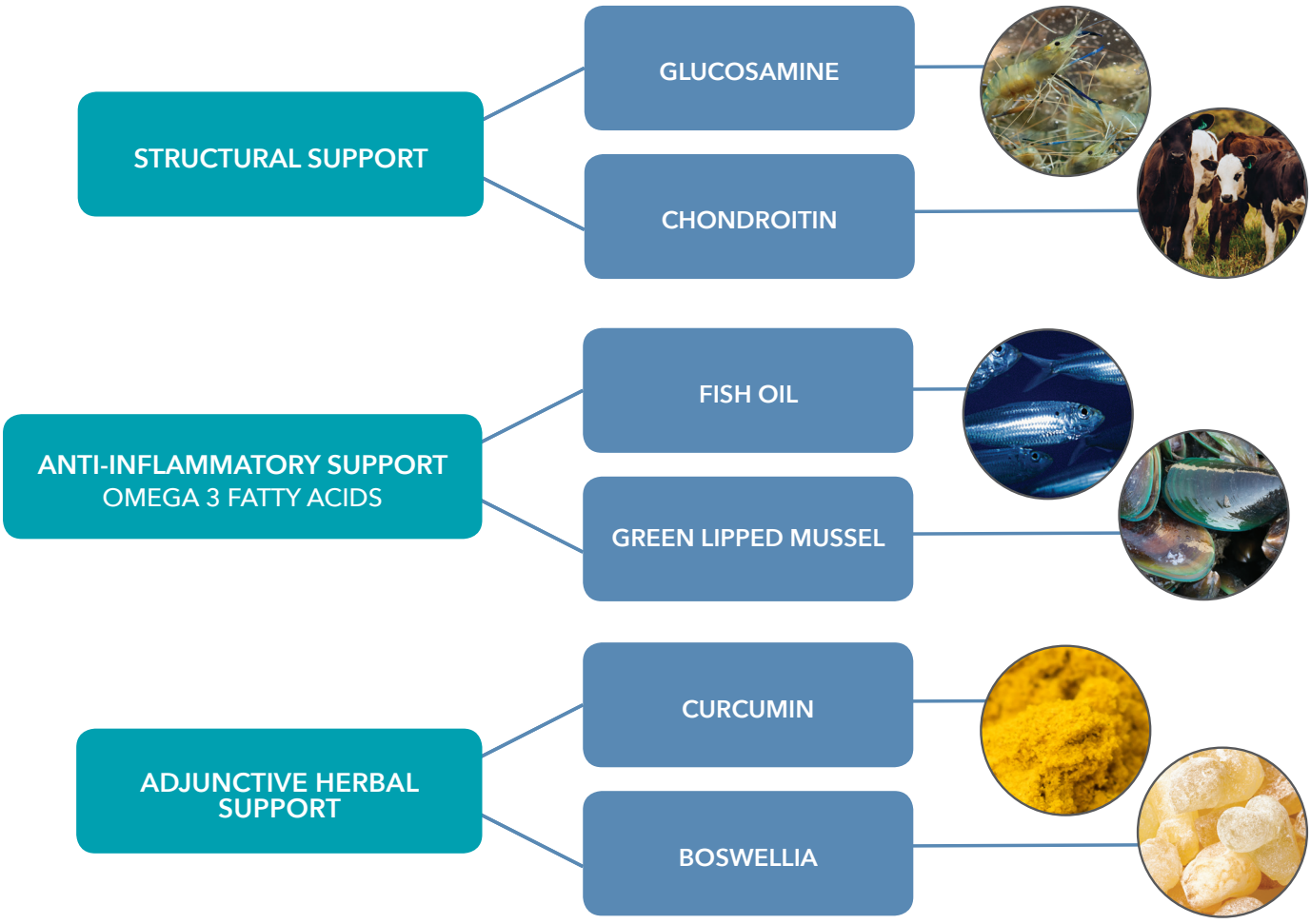
Understanding the ingredients used in nutritional supplements

The World Small Animal Veterinary Association (WSAVA) Guidelines for Recognition, Assessment and Treatment of Pain identify 3 groups of dietary supplements with potential benefits for pain management; omega-3 polyunsaturated fatty acids, glucosamine and chondroitin, and green lipped mussel (GLM).[14] While rarely used as monotherapy, herbs have also been shown to be effective when integrated into management plans for chronic medical ailments affecting companion animals.[15]

OA is a complex disease process incorporating both inflammatory and immune mediated processes which is best treated using an integrative approach.

Nutritional supplements can provide a wide array of actions to support traditional treatment protocols by:

- Providing the building blocks of cartilage (GAGs)
- Impacting the inflammatory pathways, and the biomarkers associated with pain and inflammation
- Impacting the immune mediated pathway, and the biomarkers associated with increased cartilage destruction



The actions of natural ingredients on the inflammatory pathways

When used in combination, natural ingredients have been found to block a wide array of inflammatory mediators.

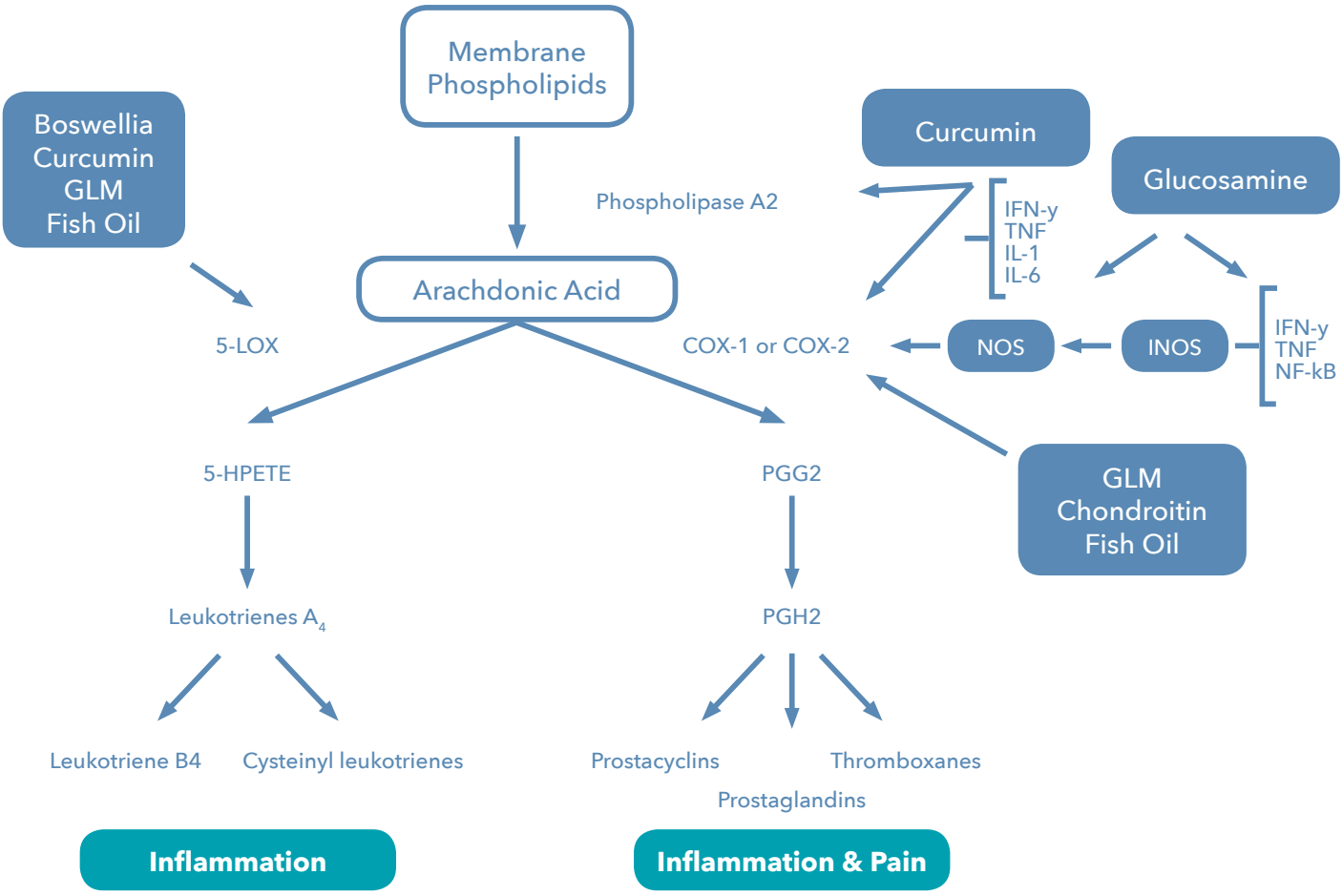


Figure 1 – The inflammatory pathways and actions of Curcumin, Boswellia, Glucosamine , Chondroitin, Fish Oil and Green Lipped Mussel.

Did you know?

Non-steroidal anti-inflammatory drugs (NSAIDs) are the competitive inhibitors of COX, the enzyme which mediates the bioconversion of arachidonic acid to inflammatory prostaglandins. Their use is associated with side effects such as gastrointestinal and renal toxicity.[16] As only the COX pathway is inhibited, Leukotriene production can be upregulated due to the arachidonate diverting through the 5-LOX pathway.[17]

Structural support

Glucosamine and Chondroitin

Glucosamine and chondroitin sulphate are components of many dietary supplements of osteoarthritis in several species. Glucosamine is a precursor of glycosaminoglycan (GAG); a building block of the extracellular cartilage matrix.[20]

Glucosamine influences the expression or activity of many mediators of OA. Actions include:

- Reduction in proteoglycan degradation
- Inhibition of the synthesis and activity of degrative enzymes and inflammatory mediators such as aggrecanases, MMPs, nitric oxide, and PGE2
- Stimulation of GAG and proteoglycan production
- Preventative effect in terms of reduction in transcription factors involved in the intracellular signalling of IL-1.

Chondroitin sulphate is the predominant component of articular cartilage and is also present within tendons, bones and vertebral discs.

Chondroitin sulphate also stimulates GAG synthesis and inhibits degrative enzyme synthesis including MMPs. It also improves synovial fluid viscosity by increasing hyaluronic acid concentrations.[9]

Clinical trials have demonstrated that the combination of Glu/CS can protect against artificially induced synovitis in dogs, to stimulate cartilage metabolism and inhibit degradation.[22]

Did you know?

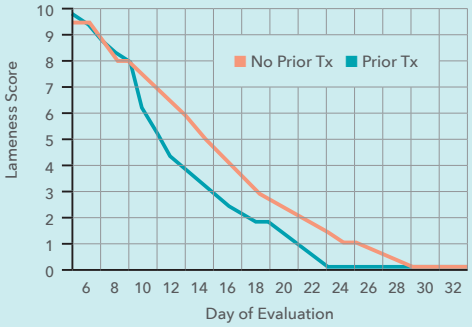
The form and source of chondroitin sulphate influences its pharmacokinetic profile. Chondroitin sulphate of bovine origin is superior to that obtained from shark cartilage because of differences in molecular mass and degree of sulfation. The molecular weight of chondroitin affects its bioavailability.[9]

In a randomised, double blind, multicentred study of 70 dogs with confirmed hip or elbow OA, dogs were administered either glucosamine & chondroitin or carprofen for 70 days.

Scale scoring assessments for pain, weight-bearing and condition were performed on days 0, 14, 42, 70 and 98. Statistically significant improvements were found for both glucosamine/chondroitin and carprofen test groups for pain, weight-bearing and condition scores.

Dogs receiving glucosamine and chondroitin experienced improvement in pain scores similar to carprofen from day 42 and also showed a carry-over effect even after treatment was stopped on day 70. [21]

In a study of 32 healthy, dogs with experimentally induced osteoarthritis, dogs treated with glucosamine & chondroitin supplementation 3 weeks prior to induction of synovitis experienced more rapid improvements in lameness after the procedure.[22]



Graph: Lameness scores of dogs that received glucosamine & chondroitin supplementation prior to induction of synovitis, against those that did not receive pre-treatment.

| Anti-inflammatory support

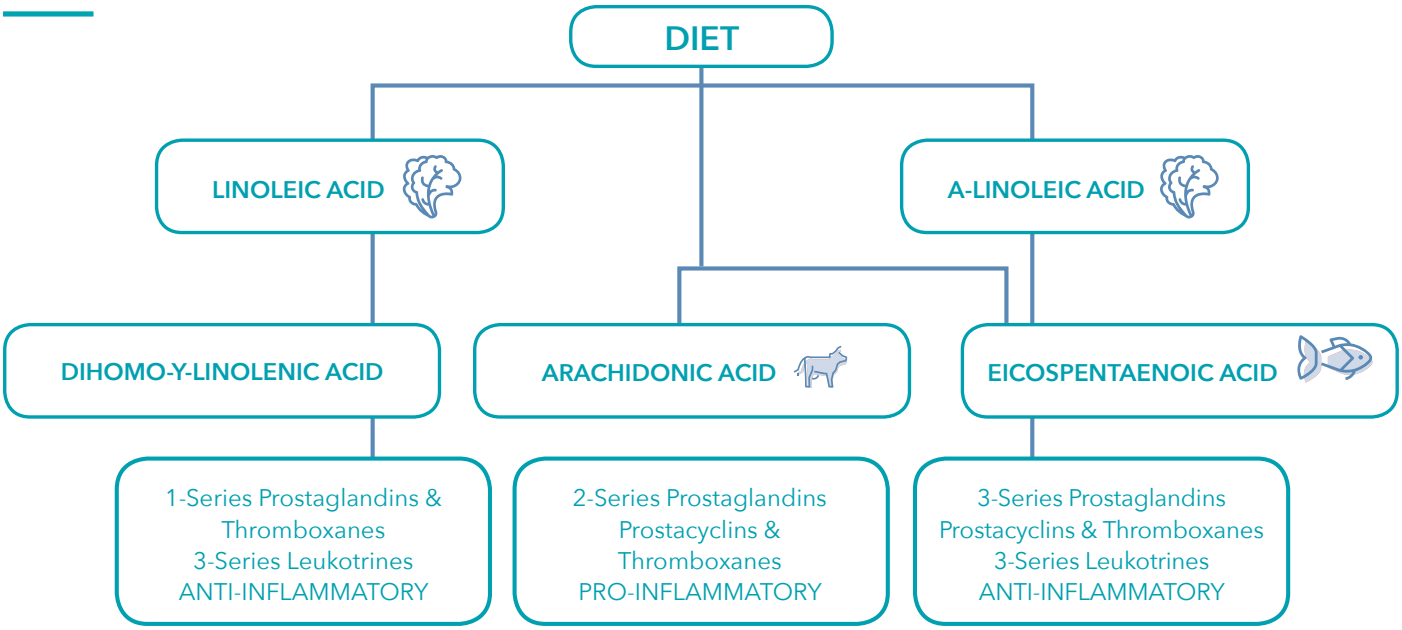
Omega 3 fatty acids

Omega-3 and omega-6 are considered essential because dogs and cats lack the enzyme to create the double bond in the omega 3 and omega 6 positions.[23] Omega-3 and omega-6 fatty acids are named for where the double bonds occur.[24]

Dietary sources of omegas 3 & 6 contain Dihomo-gamma-linolenic acid (DGLA), AA and EPA, which are incorporated into cellular membranes and are released after stimulation of the cell by inflammation, hormones or trauma. They are oxidised by COX to prostaglandins and thromboxanes, or by LOX to leukotrienes.[25]

The COX pathway causes release of essential fatty acids which then form eicosanoids. When AA is released, pro-inflammatory eicosanoids are produced. When EPA is released, anti-inflammatory eicosanoids are produced.

Dietary sources of essential fatty acids and corresponding eicosanoid formation[24]



CHARACTERISTICS OF DIFFERENT GROUPS OF PROSTAGLANDINS, THROMBOXANES & LEUKOTRIENES[31]	
1-SERIES	• **Prostaglandins:** Anti-inflammatory and inhibit platelet aggregation • **Thromboxanes:** Mildly stimulate platelet aggregation, stimulate contraction of respiratory, intestinal and vascular smooth muscle • **Leukotrienes:** Stimulate contraction of respiratory, intestinal and vascular smooth muscle
2-SERIES	• **Prostaglandins, thromboxanes and leukotrienes:** Pro-inflammatory and pro-aggregatory
3-SERIES	• **Prostaglandins:** Anti-inflammatory and inhibit platelet aggregation • **Thromboxanes:** Mildly stimulate platelet aggregation, stimulate contraction of respiratory, intestinal and vascular smooth muscle • **Leukotrienes:** Stimulate contraction of respiratory, intestinal and vascular smooth muscle

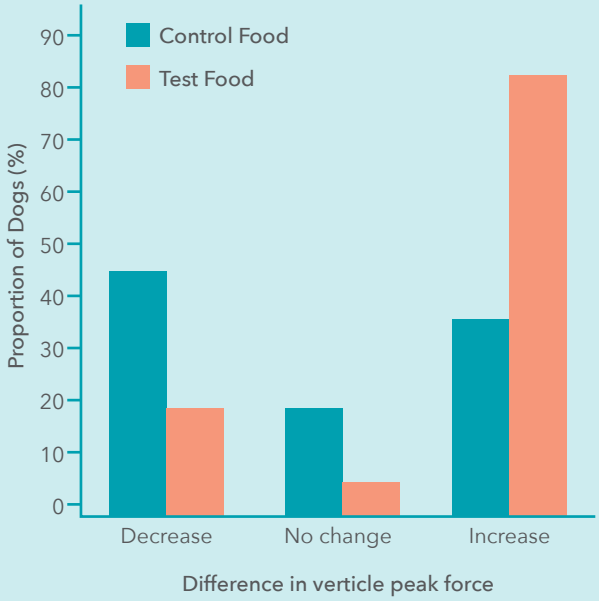
Fish Oil

Indications for EPA/DHA fish oil in the management of osteoarthritis cases:

- Mild to chronic osteoarthritis, as part of multi-modal therapy.
- Potentially as an NSAID-sparing adjunct in cases of severe osteoarthritis.[26]
- Supplementation with EPA/DHA is beneficial as it reduces PGE2 production through competition with less inflammatory prostaglandins, as well as reduction of thromboxanes that may in turn suppress proinflammatory mediators IL-1, IL-2 and TNF in cartilage.[27]

Clinical trial evaluating the effects of supplementation of fish oil on weight bearing in dogs with osteoarthritis.[28]

38 dogs with OA across 2 university clinics were assigned commercial food containing 3.5% fish oil omega-3 fatty acids (EPA/DHA). Orthopaedic evaluations and force-plate analysis of the most severely affected limb of each dog was conducted on day 0 and 90. Change in mean peak vertical force between day 0 and 90 was significant for the test-food group (5.6%) but not for the control food group (0.4%). Improvement was seen in 82% of the dogs in the test food group.



Graph 3: Proportion of dogs with an improvement in peak vertical force from day 0 to day 90.

Did you know?

Fish oil products intended for human consumption are usually formulated to 18:12 or 36:24 ratios, and are not designed for dogs. The US National Research Council recommends a 50-60% EPA and 40-50% DHA ratio for fatty acid intake for maintenance of adult dogs.

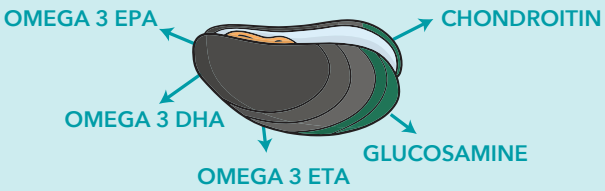
Did you know?

While the benefits of GLM are widely attributed to its lipid content, GLM also contains many other potentially beneficial nutrients including glycoaminoglycans (chondroitin sulphate), vitamins E & C, zinc, copper and manganese.[35]

Green Lipped Mussel (Perna canaliculus)

Green-lipped mussel (GLM) is endemic to the coastal waters of NZ and has long been recognized for its anti-inflammatory benefits. GLM contains a range of bioactive lipids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), eicosatetraenoic acid (ETA), alongside anti-oxidants and glycosaminoglycans (GAG).[29]

Active components of the Green Lipped Mussel



Chemical structure of ETA & Arachidonic acid[30]

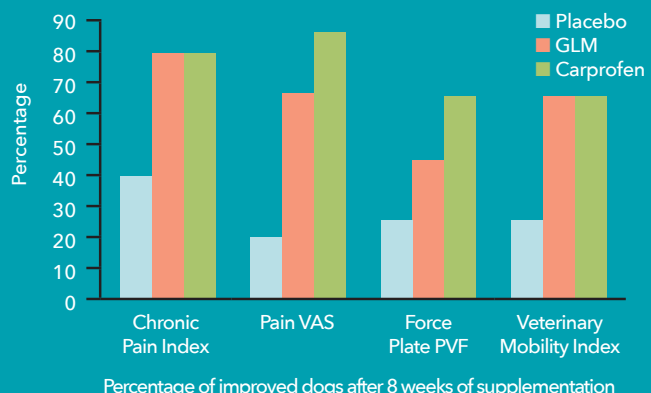
It has been identified that the predominant bioactive poly-unsaturated fatty acid (PUFA) of GLM, ETA is very similar to the molecular structure of Arachidonic acid (AA).

7, 11, 14, 17-eicosatetraenoic acid (C20:4, 68%)

5, 8, 11, 14-eicosatetraenoic acid (arachidonic acid)

The interrupted bond positioning of this structural analogues of AA may account for its anti-inflammatory behaviour, by competitively inhibiting the active site of enzymes which use AA as a substrate. i.e. LOX and COX, thereby reducing the production of leukotriene (LT) and prostaglandin (PG) metabolites.[30]

In a study of 45 dogs with chronic pain and osteoarthritis, divided into 3 treatment groups & given carprofen, placebo or GLM, by week 8, dogs in the carprofen and GLM groups showed 80% improvement in the owner evaluated chronic pain index and 67% in the veterinary mobility index.[31]



Graph 4: percentage of improved dogs using different assessment methods after 8 weeks of treatment on a placebo, GLM or carprofen.

Adjunctive herbal support

Curcumin

Curcumin is the key active component of the spice turmeric and has been shown to possess potent anti-inflammatory and antioxidant properties.[11]

Anti-inflammatory activity of curcumin

Curcumin has been shown to inhibit multiple inflammatory mediators (inc. PLA2, COX-2 and 5-LOX) in cultured cells and has also been found to inhibit NF-kB- dependent gene transcription in articular chondrocytes (fig. 1).[11] In vivo canine studies have also displayed curcumin's ability to reduce TNF-α & IL-1.[32]

Anti-oxidant activity of curcumin

Cartilage degradation is accelerated by matrix metalloproteinases (MMPs) and reactive oxygen species (ROS). MMP's are promoted by inflammatory cytokines and degrade ECM, including collagen and proteoglycans.

In vitro studies have indicated curcumin's antioxidant ability, displaying effective scavenging of ROS and reactive species. In vivo it may have indirect antioxidant properties linked to its ability to inhibit inflammatory enzymes like MMP or via enhanced glutathione synthesis.[11]

Did you know?

In its pure form, the bioavailability of curcumin may be limited. Therefore, different strategies are required to improve the absorption of curcumin.[11] Formulations including a phospholipid complex have been shown to increase absorption by 29- fold when compared to curcumin on its own.[33]

SUMMARY OF THE BIOLOGICAL ACTIONS OF CURCUMIN ON HUMAN AND ANIMAL JOINT TISSUE [11]

ANTIOXIDANT EFFECTS

- Scavenger of reactive oxygen and nitrogen species in vitro
- Inhibits IL-1b-induced NO production by bovine and human chondrocytes and human cartilage explants
- Inhibits IL-1b-induced superoxide dismutase activity in bovine chondrocytes in monolayer

ANTI-INFLAMMATORY EFFECTS

- Inhibits NF-kB-dependent gene transcription in chondrocytes
- Inhibits COX-2, but not COX-1, gene expression in IL-1b-treated bovine chondrocytes in monolayer
- Inhibits IL-6 and IL-8 gene expression by bovine and human chondrocytes
- Inhibits IL-6, IL-8 and PGE2 production by human chondrocytes and cartilage explants

ANTI-CATABOLIC EFFECTS

- Decreases cell viability of adherent synoviocytes
- Inhibits IL-1b-induced glycosaminoglycan (GAG) release from canine and human OA cartilage explants
- Decreases MMP-3 synthesis in chondrocytes in alginate beads and in human cartilage explants
- Suppresses IL-1b and OSM-induced MMP-1, MMP-3, MMP-9 and MMP-13 gene expression by human chondrocytes via inhibition of NFkB activation and nuclear translocation

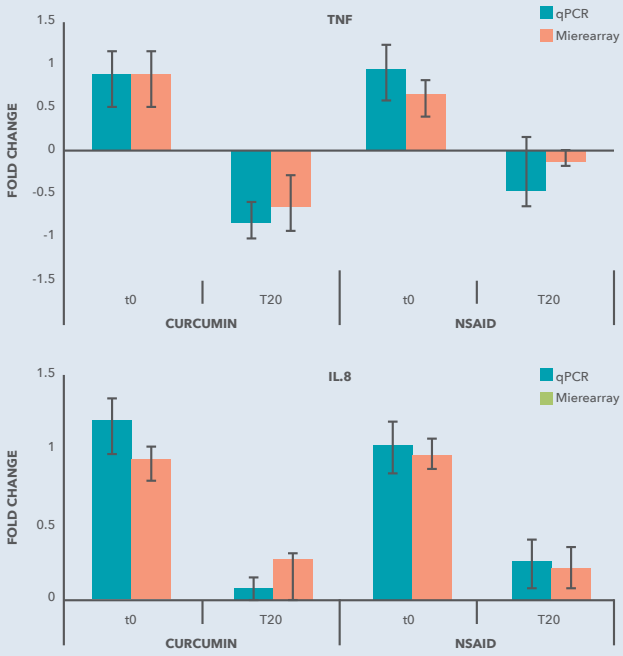
ANABOLIC EFFECTS

- No effect on aggrecan production by human chondrocytes in alginate beads
- Decreases proteoglycan mRNA expression in bovine chondrocytes in monolayer
- Reverses the IL-1b-induced inhibition of type II collagen and b1-integrin gene expression in human chondrocytes

Table 1: extract from 'Henrotin *Biological Actions of Curcumin on Articular Chondrocyte* (2010)', outlining the various biological actions of curcumin on human & animal joint tissue

Twelve OA affected dogs were randomly assigned to two groups. Group one was treated with curcumin & the second group was treated with the NSAID firocoxib. After 20 days both NSAID and curcumin treatments reduced pro-inflammatory cytokine tumour-necrosis factor alpha (TNF-α). Furthermore, unlike firocoxib, curcumin administration was shown to downregulate the inflammatory mediator interleukin-8 (IL-8).[32]

Graph 4 & 5. mRNA expression of selected genes as determined by real time PCR and microarray analyses. The gene expression level determined by real time PCR was normalised to geometric mean of BACT and MRPS7. Error bars indicate ±SD.



Boswellia

Boswellia serrata is a tree found in India, Northern Africa, and in the Middle East. Strips of boswellia bark are peeled away, yielding a gummy oleo-resin. Extracts of this gummy exudate have been traditionally used (in the Ayurvedic system) as an anti-arthritic, astringent, stimulant, expectorant and antiseptic.

Boswellia has been demonstrated to be effective in alleviating the clinical signs of OA in dogs.

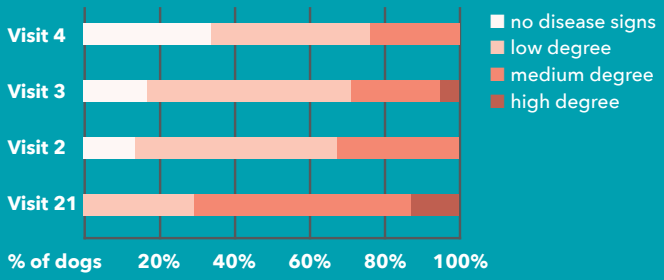
In vitro testing has shown that boswellia blocks the synthesis of pro-inflammatory 5-LOX products.

Pharmacological and clinical studies have confirmed that boswellia resin can inhibit a branch of the arachidonic acid cascade related to leukotriene synthesis, without affecting prostaglandin synthesis. It is assumed that excessive production of leukotrienes is responsible for maintenance of a chronic inflammation process and that inhibition may down regulate the process of disease.[36]

Did you know?

Boswellic acid is mainly responsible for many of the pharmacological effects of the *Boswellia serrata* tree, including its anti-inflammatory activity.[34] Look for the Boswellic acid content when recommending this ingredient.

29 dogs suffering from osteoarthritis or dysplastic joint disease were selected for a study based on physical examination, history and radiographs. The daily meal of each dog was supplemented with a standardised extract of boswellia resin at 400 mg per 10 kg per day for 6 weeks. In 71% of dogs there was a significant improvement in most evaluated clinical signs. In addition, the frequency of external factors; "lameness when moving" and "lameness after a long rest" decreased in frequency throughout the 6-week period.[36]



Graph: Changing degrees of the clinical disease state of osteoarthritis in the efficacy population before, during and after treatment with boswellia resin observed between visits 1, 2, 3 & 4.

Deciding which PAW joint care product to recommend

Is the dog showing symptoms of osteoarthritis?

- ☐ Lameness
- ☐ Reluctance to exercise or jump
- ☐ Weight gain
- ☐ Stiffness
- ☐ Pain when touched in certain places (legs, hips, spine)

YES...

Is the pain mild-moderate or moderate-severe?

YES...

Start the dog on a **glucosamine & chondroitin supplement** daily to help nourish and support the joint cartilage and delay the onset of osteoarthritis and it's associated symptoms.

Try recommending:

NO...

Could the dog be predisposed to osteoarthritis later in life?

- ☐ Large or giant breed dog
- ☐ Highly active lifestyle
- ☐ Breed known to suffer from conformation concerns

NO...

Is the dog >5 years of age?

YES...

Start the dog on a **glucosamine & chondroitin supplement** daily to help nourish and support the joint cartilage and delay the onset of osteoarthritis and it's associated symptoms.

Try recommending:

NO...

The dog likely doesn't need any intervention at this point in time - reassess when the dog reaches 5 years of age

Osteoarthritis affects cats too

82% of cats over the age of 14 have osteoarthritis in at least 1 joint. Signs to look for include:

- ☐ Sleeping more often to avoid movement that causes pain.
- ☐ Being extra aloof or cranky due to pain.
- ☐ Finding it difficult to jump onto furniture.
- ☐ Making a mess when they use their litter tray.

Start the cat on a **green lipped mussel supplement** to reduce inflammation.*

Try recommending:

Moderate-severe

As part of a multi modal treatment plan (inc, healthy lifestyle, immediate pain relief & surgical intervention where needed) start the dog on a **glucosamine & chondroitin supplement** daily to help nourish and support the joint cartilage, in conjunction with a combination of natural anti-inflammatory ingredients such as **green lipped mussel, curcumin & boswellia** to reduce the severity of the associated pain *

Try recommending:

Mild-moderate

Does the dog lead a healthy lifestyle?

- ☐ Healthy weight
- ☐ Moderate/low impact exercise
- ☐ Premium diet

NO

Adress lifestyle issues:

- ☐ Reduce weight
- ☐ Begin low impact exercise routine
- ☐ Change diet

Start the dog on a **glucosamine & chondroitin supplement** daily to help nourish and support the joint cartilage and delay the onset of osteoarthritis and it's associated symptoms. **Try recommending:**

In conjunction with a **green lipped mussel** OR **fish oil supplement** to reduce inflammation and associated pain whilst lifestyle concerns are being addressed.
Try recommending:

Reassess pain once ideal weight and exercise are acheived.

YES

As part of a multi modal treatment plan (inc, healthy lifestyle, immediate pain relief & surgical intervention where needed) start the dog on a **glucosamine & chondroitin supplement** daily to help nourish and support the joint cartilage, in conjunction with a combination of natural anti-inflammatory ingredients such as **green lipped mussel, curcumin & boswellia** to reduce the severity of the associated pain *

Try recommending:

* review role of NSAIDs/disease modifying drugs if immediate pain relief is required
* this flow-chart is designed to be used in conjunction with a multimodal treatment protocol where pharmaceutical intervention may be required as an adjunct to natural therapies

References

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