The Facts and Opinions on Joint Supplements

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Objectives: Review the current evidence on the use of joint supplements for management of canine osteoarthritis. Supplements that will be discussed will include the use of omega-3 fatty acids, green lipped mussel powder, glucosamine, chondroitin sulfate, and avocado/soybean unsaponifiables among others.

Canine Osteoarthritis

- Generally is secondary to a developmental or acquired musculoskeletal disorder
- An estimated 20% of adult dogs are affected by OA.

Polysulfated glycosaminoglycan (PSGAG)[1]

- PSGAGs are FDA-regulated and are NOT a nutraceutical
- Adequan Canine ® is an FDA-licensed drug
    - Licensed for intramuscular injection for the control of signs associated with non-infectious degenerative and/or traumatic arthritis of canine synovial joints
    - Semi-synthetic glycosaminoglycan prepared by extracting glycosaminoglycans (GAGs) from bovine tracheal cartilage
- Administration
    - Best started in early stages of OA as it is a chondroprotective agent
    - 2mg/lb injected intramuscularly twice weekly for 4 weeks
- Proposed effects of treatment:
    - Reduction in proteoglycan degradation
    - Inhibition of synthesis and activity of aggrecanases, matrix metalloproteinases (MMPs), nitric acid, and PGE2
    - Stimulation of GAG synthesis
    - Increased hyaluronan concentrations

Nutraceuticals

- Definition: Nondrug substance produced in a purified or extracted form and administered orally to provide agents required for normal body structure and function, with the intent on improving health and wellbeing.[1]
    - No mention of being “scientifically proven”
- More than 30 nutraceutical products have been listed as potentially active in osteoarthritis[1]

- Not closely regulated by the FDA[1]
- Cannot have label claims for treating, curing, or mitigating disease[1]
- Many are least-cost formulations and quality assurance is lacking to nonexistent[1]
- Fall short in evidence-based efficacy, lack dose titration studies to validate appropriate doses of individual products, and have shown inconsistencies of produce quality assurance.[1]
- All nutraceuticals are NOT created equal[1]
- Product selection should be determined by the ACCLAIM criteria[1,2]
    - A = A name you recognize?
    - B = Clinical experience
    - C = Content
    - L = Label claims
    - A = Administration recommendations
    - I = Identification of lot
    - M = Manufacturer information
- Safety Issues
    - Contamination[2]
        - Pesticides, heavy metals, toxins, dimethyl sulfoxide (DMSO), and viruses have been identified in some nutritional products

<u>Omega-3 Fatty Acids</u>

- Proposed mechanism of action (MOA)
    - Essential fatty acids are a group of polyunsaturated fatty acids that contain both omega-6 fatty acid arachidonic acid (AA) and the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[1] Arachidonic acid is incorporated into cell membranes, which are broken down in osteoarthritic joints.[1] When metabolized, it yields inflammatory components, such as prostaglandins, leukotrienes, and thromboxanes. The omega-3 fatty acids are able to compete with and replace omega-6 fatty acids in cell membranes, thus reducing the inflammatory response.[1]
- Administration
    - Optimum dietary n6:n3 ratio is unknown[1]
- Proposed clinical outcomes of treatment[1]
    - Improved owner perception of comfort and function
    - Improved weight bearing in the affected limb
    - Decreased need for NSAIDs

Green lipped muscle powder (GLMP; Perna canaliculus)

- Contains a unique omega-3 fatty acid, eicosatetraenoic acid (ETA), which appears to act as a dual inhibitor of arachidonic acid oxygenation by both the cyclooxygenase and lipoxygenase pathways.[3]
- 6 of 7 studies in dogs treated with greenshell muscle extract showed beneficial effects for alleviating symptoms of osteoarthritis.[4]

Glucosamine/chondroitin

- Definitions
    - Glucosamine is an amino monosaccharide that, once modified as N-acetylglucosamine, is proposed to act as a precursor of the disaccharide units of GAGs such as hyaluronan and keratin sulfate.[1]
    - Chondroitin sulfate is a GAG consisting of alternating disaccharide subunits of glucoronic acid and sulfated N-acetylgalactosamine. Chondroitin sulfate is a normal constituent of cartilage.[1]
- Proposed MOA
    - Glucosamine[1]
        - Stimulation of GAG synthesis
        - Inhibition of cyclooxygenase independent anti-inflammatory properties
        - Inhibition of IL-1 stimulated gene expression of protease expression
    - Chondroitin sulfate[1]
        - Stimulation of synthesis of PG
        - Inhibition of degradative enzymes and inhibition of IL-1 stimulated gene expression
        - Inhibition of production of pro-inflammatory genes including MMPs
- Administration[1]
    - Best used in combination?
        - Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) in humans showed that only the combination of glucosamine and chondroitin was efficacious for the reduction of pain and only in those with moderate to severe OA
        - Combining glucosamine, chondroitin sulfate, and manganese ascorbate has shown improved in vitro effects in suppressing several major inflammatory mediators of osteoarthritis
    - Oral absorption concerns in dogs
        - Pharmacokinetic studies in dogs reveal that glucosamine hydrochloride is only 10-12% bioavailable from single of multiple doses
        - 12% bioavailability for glucosamine and 5% for chondroitin
- Overall, based on the available literature, the potential benefits of glucosamine and chondroitin use in osteoarthritic canines can neither be confirmed nor denied.[3] The

available evidence is also difficult to interpret due to the use of different manufacturers, salt forms, compositions, sources, strengths, regimens, therapy durations, and combinations of active ingredients.[5]

Avocado/Soybean Unsaponifiables (ASU)

- Definition
    - ASUs are plant extracts derived from unsaponifiable residues of avocado and soya bean oils, commonly mixed at a ratio of one-third to two-thirds, respectively.[6]
    - ASU contain many compounds including fat-soluble vitamins, sterols, triterpene alcohols, and possibly furan fatty acids.[6]
- Proposed MOA[1]
    - Prevent inhibitory effect on subchondral osteoblasts on aggrecan synthesis
    - Inhibits cartilage degradation and promotes cartilage repair
    - In vitro effects in suppressing several major inflammatory mediators of osteoarthritis including MMP-13, inducible nitric oxide synthase (iNOS), tumor necrosis factor alpha (TNF-α), IL-1β, and COX-2.
- Dasuquin® is a ASU-rich product
- Possible synergistic effect with combined administration of epigallocatechin gallate (EGCG)[1]
    - EGCG is the major anti-oxidant in green tea
- Only a few studies have evaluated in vivo efficacy of ASU in dogs with induced osteoarthritis.[6] Additional studies are needed to support the effectiveness of ASU in naturally occurring canine OA.[6] Additionally, data is needed concerning the concentrations of ASU achieved in the blood after administration.[6]

Boswellia serrata extract

- Boswellia trees and shrubs are native to tropical regions of Africa and Asia[1]
- Works synergistically with ASU+glucosamine+chondroitin sulfate to suppress the production of PGE2 in IL-stimulated cell cultures[1]
- An open multicenter veterinary clinical trial of dogs with manifestations of chronic joint and spinal disease treated with Boswellia resin showed a reduction in lameness, local pain, and stiffness compared to baseline but there was no placebo group.[6]

Turmeric (Curcuma longa; P54FP extract)

- Perennial plant of the ginger family, native to southwest India and Southeast Asia[1]

- One active ingredient of turmeric is curcumin which offers anti-inflammatory effects through inhibition of I kappa B kinase (IKK) of the NF-κB signaling pathway and through down-regulation of COX-2 and iNOS by suppression of NF-κB[1]
- Evidence for use with canine osteoarthritis is sparse and controversial.

Phycocyanin

- Composed of two protein subunits with covalently bonded phycobilins that are the light-capturing part of the blue pigment in blue-green algae[1]
- Active agent in PhyCox®
- C-phycocyanin is a selective COX-2 inhibitor[1]
- Shown to have anti-oxidant and anti-inflammatory properties in vitro and in vivo in rodents[1]
- The C-phycocyanin-based nutraceutical and constituents (PhyCox®) displayed similar strength to carprofen in reducing TNF-α, IL-6, MMP-3, nitrate, nitrite, and sGAG production in an in-vitro canine chondrocyte model of osteoarthritis.[7] Further in vivo investigation is indicated.

References

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