When More Is Needed: Nutraceuticals

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Supplementation of diets may be necessary due to dietary imbalances or because of disease-specific therapeutic benefits of the supplement. Supplements are often used with homemade diets to help create a complete and balanced diet or to increase the intake of a therapeutic compound that may be present in the diet, but at less-than necessary levels. Medical treatments for chronic disease problems often include advice concerning diet. Additionally, many dietary supplements are available for sale, some of which make health claims although they are not supposed to. These compounds may be sold as "nutraceuticals", or as "alternative" or "complementary" therapies. Complementary and alternative therapies are not intrinsically better or worse than conventional treatments, they are just different. Use of such therapy does not absolve one of the responsibilities to be a thoughtful, informed consumer, and caregiver to a pet. One of the many challenges facing caregivers today is finding and interpreting information that permits them to decide the proper role of these popular, sometimes heavily advertised and lucrative products.

The Dietary Supplement Health and Education Act of 1994 established a framework for labeling and providing information about nutrition-related products, herbs, and other botanicals. The act permits labels to contain a statement describing how the product affects structure and function or general well-being in humans, but not to make specific health claims. The label must carry a disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

The AVMA defines nutraceuticals as "…micronutrients, macronutrients and other nutritional supplements" used as therapeutic agents. The AVMA Guidelines for Complementary and Alternative Veterinary Medicine further states: "Claims for safety and effectiveness ultimately should be proven by the scientific method. Circumstances commonly require that veterinarians extrapolate information when formulating a course of therapy. Veterinarians should exercise caution in such circumstances."

The National Animal Supplement Council (NASC) has developed a proposal to attempt to allow continued marketing of unapproved "nutraceutical" ingredients. Its proposal would:

- Establish a reporting system for events in which supplements may have caused side effects,
- Require NASC members to adopt manufacturing and quality controls,
- Fund research so ingredients would meet AAFCO's ingredient definition process, and
- Start a self-policing enforcement program to ensure labels are accurate and do not include drug claims.

The proposal identified five non-approved ingredients for which the NASC will seek an AAFCO feed ingredient definition. These are glucosamine, chondroitin sulfate, MSM, garlic and *Rehmannia*.

NUTRACEUTICALS FOR OSTEOARTHRITIS (AND OTHER USES)

In clinical practice using nutraceuticals can be part of multimodality management of patients who have had musculoskeletal trauma, orthopedic surgery for DOD, patients at risk for DOD, and geriatric patients with OA. Understanding the physiological and pathophysiological mechanisms involved may aid in selecting individual nutraceuticals that will optimize patient management. Traditionally OA has been regarded primarily as a degenerative process and most often a consequence of aging. Treatments focused solely on symptomatic management rather than halting disease progression will fail as research revisits the role of inflammation in OA. The same inflammatory cytokines that drive rheumatoid arthritis have been shown in OA including IL-1, IL6, and TNFα. Studies suggest IL-1β and TNFα occupy a key role in the development of OA, with elevated levels of these cytokines or their gene expression reported in synovial tissues, synovial fluid and/or plasma. Investigating the role of an individual nutraceutical in maintaining the balance in the OA niche and attendant inflammatory milieu can be used as a regenerative

strategy for bone or cartilage in OA. This requires individual patient evaluation with a complete history, current activity level, nutrition, environmental factors, laboratory test, radiographs and/or other diagnostics.

A review of nonsurgical management of hip dysplasia using an evidence classification proposed by Aragon and Budsberg found fourteen articles meeting their criteria with three nutraceutical studies, two providing Level II evidence and one providing Level III evidence. The nutraceuticals in the studies are classified as antioxidants and chondromodulating agents that are purported to slow or alter the progression of osteoarthritis. Chondromodulating agents can be further divided into agents approved by the US Food and Drug Administration, such as parental polysulfated glycosaminoglycans such as Adequan and Pentosan, which can have label claims of clinical effect. The other type of chondromodulating agents are oral or nutritional supplements, which are not regulated, and legally cannot claim any medical benefit. These oral nutraceuticals include glucosamine and chondroitin sulfate.

Glycosaminoglycans

Glucosamine is an amino sugar and precursor for biochemical synthesis of glycosylated proteins and sugars. Glucosamine-6-phosphate synthesized in the hexosamine pathway results in the production of UDP-N-acetylglucosamine, which is used for making glycosaminoglycans, proteoglycans, and glycolipids. Glycosaminoglycans are a major component of joint cartilage; therefore, it is believed that supplemental glucosamine may rebuild cartilage. *In vitro* studies support this claim although these studies use concentrations not achieved in serum or plasma after oral administration. Results of studies of chondromodulants both in veterinary and human literature are mixed due to product used (glucosamine alone, glucosamine/chondroitin sulfate), dose administration, subjective and objective measurements of outcome, and length of trials. In a randomized, double blind, placebo controlled clinical trial comparing glucosamine/chondroitin sulfate to carprofen in 35 dogs with OA, carprofen treated dogs had improvement in 5 subjective measures while dogs treated with the glucosamine/chondroitin sulfate improved in 3 of 5 measures, but only after final assessment at 70 days. A 60-day, prospective, randomized, double blind, placebo controlled trial of 71 dogs comparing carprofen, meloxicam, glucosamine/chondroitin, and placebo demonstrated significant improvement in objective measurements with carprofen and meloxicam but not with the nutraceutical or placebo. Based on these studies and others the clinical evidence of these chondromodulants seems weak and will most likely be dependent on content, amount of disease, dosing, and length of treatment. Another natural source of glycosaminoglycans, the New Zealand green lipped mussel (*Perna canaliculus*), is marketed for its chondromodulating effects. Numerous publications reporting the results of uncontrolled studies have been published with promising results. In reviewing the studies of green lipped mussel extract as beneficial in treating canine OA, results seem promising, but there are uncertainties with the scientific quality of the data published.

Glycosaminoglycans are found on the mucosal surface of all epithelial lined organs such as the respiratory, intestinal, and urinary tract. Their use has been recommended for prevention of microbial invasion, e.g., bacterial urinary tract infection. While this is based on sound theoretical reasoning, there are no studies to demonstrate the effectiveness of glycosaminoglycans for managing patients with bacterial urinary tract infections. Pentosan polysulfate sodium, a polysulfated glycosaminoglycan, has been shown in randomized controlled clinical trials in women to be beneficial (35% response versus 9% with placebo); however, the few studies in cats with idiopathic cystitis have failed to show a benefit (pentosan polysulfate sodium or N-acetylglucosamine).

Avocado/Soybean Unsaponifiables

Avocado/soybean unsaponifiables (ASU) are composed of the unsaponifiable fractions of avocado and soybean oils in a 1/3 to 2/3 proportion. ASU has anti-OA properties by inhibiting interlukin-1 and stimulating collagen synthesis in cartilage cultures. Human clinical trials have shown some beneficial effects of ASU on clinical symptoms of OA, but conflicting data in other studies found no long term benefits. In one study of dogs, OA was induced by anterior cruciate ligament transection. Dogs then received placebo or ASU (10 mg/kg/24h). The size of macroscopic lesions of the tibial plateau, severity of cartilage lesions, synovial cellular infiltration, and inducible nitric oxide synthase were decreased

significantly and there was reduced loss of subchondral bone volume and calcified cartilage thickness in the group receiving ASU.

Zeel®

Zeel® is an over-the-counter preparation that has been evaluated in 2 controlled studies in dogs. This is a highly diluted proprietary formulation of herbs, metabolites, minerals, and antioxidants. In a study of 68 dogs greater than one year of age diagnosed with OA, it was compared with carprofen in a multicenter, prospective, observational open-label cohort study in 12 German veterinary clinics. In another study in dogs (n = 44), greater than one year of age diagnosed with OA, it was compared with carprofen and a placebo. Clinical signs and several measures of OA improved significantly with treatment in both studies; however, in one study, it was not as effective as carprofen. The composition of the products and the dosage of Zeel® differed between the two studies, which confounds interpretation of results.

Boswellia serrata

Boswellia or Indian frankincense, comes from the *Boswellia serrata* tree. Resin from the bark of this tree is purported to have anti-inflammatory properties derived primarily from 3-O-acetyl-11-keto-β-boswellic acid (AKBA), which inhibits 5-lipoxygenase and matrix metalloproteinases, and decreases tumor necrosis factor α and interleukin 1β. *Boswellia* resin has been shown to improve clinical signs and pain in humans in controlled studies. *Boswellia* resin has been evaluated in 24 dogs in an open multi-center study. Improvement in clinical signs, lameness, and pain was found in 17 of 24 dogs.

Methylsulfonylmethane (MS)

Methylsulfonylmethane (MSM, or dimethylsulfone) is an organic sulfur compound belonging to a class of chemicals known as sulfones. It occurs naturally in some primitive plants and is present in small amounts in many foods and beverages. MSM is also known as $DMSO_2$, a name that reflects its close chemical relationship to dimethyl sulfoxide (DMSO), which differs only in the oxidation state of the sulfur atom. MSM is the primary metabolite of DMSO in humans, and it shares some of the properties of DMSO. MSM is sold as a dietary supplement that is marketed with a variety of claims and is commonly used (often in combination with glucosamine and/or chondroitin) for helping to treat or prevent osteoarthritis. Retail sales of MSM as a single ingredient in dietary supplements amounted to $115 million in 2003.

Omega 3 (n-3) Fatty Acids

The potential of modifying the inflammatory components of osteoarthritis using nutritional components is another approach of nutraceutical therapy. Arachidonic acid, an n-6 fatty acid, is incorporated into cell membranes and when metabolized, yields the 2 and 4 series of prostaglandins, leukotrienes and thromboxanes. These pro-inflammatory pathways are where conventional drugs are used to control OA inflammation. Substituting n-3 fatty acids into cell membranes may decrease inflammation with biosynthesis of eicosanoids of the 3 and 5 series, which are less pro-inflammatory. In addition to modulating cytokines, n-3 fatty acids have been shown to reduce expression of cyclooxygenase 2-lipoxygenase-5, aggrecanase, matrix metalloproteinase 3 and 13, interleukin 1α and 1β, and tumor necrosis factor α. Interestingly n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to decrease inflammatory exudates in tissues through production of oxygenated products called resolvins (resolution phase interaction products) and docosatrienes. There is growing data showing the positive effects of n-3 fatty acids supplementation on cartilage metabolism with degradative enzymes and reducing inflammatory responses elicited by chondrocytes and joint matrix during the progression of OA. An unpublished study was performed in dogs evaluating omega 3 fatty acids and experimentally induced stifle OA. Dogs were randomly assigned to isocaloric diet groups containing 21.4% fat (dry matter basis, DMB) differing only in fatty acid composition: a diet with an n-6 to n-3 ratio of 28:1, 8.7:1 (control diet) and a diet with an n-6 to n-3 ratio of 0.7:1. Dogs began the new diet 3 months prior to surgical transection of the left cruciate ligament, were continued on the diet for 6 more months prior to surgical repair, and maintained for 12 months following repair. When compared to the high n-6 diet and control diet, the high n-3 diet was associated with lower serum cholesterol, triglycerides, and phospholipids, lower synovial concentration of prostaglandin E2, better ground reaction forces, and less radiographic changes of OA.

Omega-3 fatty acids have been shown to be helpful with other inflammatory conditions such as dermatological disorders, intestinal disorders, and feline idiopathic cystitis. Dosing of the omega-3 fatty acids is important and should be based on the sum of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as these are the biologically active omega-3 fatty acids. Bauer has published a table with suggested dosages based on physiologic or disease status; however, a beginning dose of 300 mg of EPA+DHA per 10 pounds every 24 hours is reasonable. It is important that clients understand that the dosage is based on the EPA+DHA in the product. For example, many over the counter fish oil capsules contain 1,000 mg of omega-3 fatty acids of which 300 mg is EPA+DHA. GNC makes several 'triple strength' products that contain more concentrated EPA+DHA as does Snip-Tips and Eicosaderm pump. Begin with half of the calculated dose for the first 1 to 2 weeks and then increase to the final dose if tolerated as some animals develop diarrhea when given fish oil.

NUTRACEUTICALS FOR GASTROINTESTINAL DISEASE (AND OTHER USES)

Anti-Oxidants

Anti-oxidants refer to a heterogeneous group of compounds that prevent free-radical damage to cell membranes. They may be beneficial with inflammatory diseases, aging, and certain cancers. While many studies failed to document benefit of a single anti-oxidant, more recent evidence suggests that utilizing a balanced, mixed source of antioxidants may provide benefit with certain diseases. A PubMed search on "antioxidants" and "controlled clinical trial or clinical trial" returned 28 citations. Anti-oxidant treatment improved cardiac functional parameters in dogs with chronic valvular disease, decreased cataract formation when applied topically, increased immune responsiveness to vaccination in young dogs, increased cognition in aged beagles, increased immune-responsiveness in healthy geriatric dogs, decreased oxidative stress of acetominophen on feline erythrocytes, and improved joint function and pain in dogs with arthritis; however, they failed to ameliorate muscle damage in sled dogs, Antioxidants may be beneficial with certain types of cancer, but controlled studies are lacking in dogs and cats.

S-adenosylmethionine (SAMe) is a co-substrate involved in transmethylation, transsulfuration, and aminopropylation reactions, which occur primarily in the liver. In controlled trials of humans with osteoarthritis, SAMe is as effective as non-steroidal anti-inflammatory drugs and better than placebo in reducing pain and in improving function with a lower likelihood of side-effects; however, no difference with a non-steroidal anti-inflammatory drug was found in one study. A systematic review was inconclusive and was hampered by inclusion of small trials of questionable quality. A six week RCCT of 33 dogs blocked by body condition score were assessed using pressure platform gain analysis, examinations score, goniometry, and Canine Brief Pain Inventory (CBPI). Data collected did not support the use of SAMe as a single treatment for reducing clinical signs of OA.

Milk Thistle

Milk thistle is a European medicinal plant that contains silimarin (sylmarin, silibinin, sylibin). It is used with hepatobiliary disease because it thought to possess anti-oxidant activity, increase hepatic protein synthesis, stabilize hepatocellular membranes, chelate iron, and alter cholesterol metabolism. There are no published controlled clinical studies in dogs and cats. One experimental study documented anti-toxic effects of silibinin against deathcap fungus (*Amanita*) in dogs. Recommended dosages are 50–250 mg/day or 20–50 mg/kg/day. The active components of milk thistle are used for treatment of liver disease.

A study examined the protective effects of a combination of S-adenosylmethionine (SAMe) and silybin (Denamarin, Nutramax Laboratories, Edgewood, MD, USA) for lomustine (CCNU)-induced hepatotoxicity in 50 dogs. Dogs with lymphoma, a mast cell tumor, or histiocytic sarcoma and a normal alanine aminotransferase (ALT) activity were enrolled and prescribed CCNU with or without corticosteroids. Dogs were prospectively randomized to receive either concurrent Denamarin during CCNU chemotherapy or to receive CCNU alone, and plasma biochemical analysis was performed before each dose. More dogs receiving CCNU alone had an increase in ALT activities than dogs receiving CCNU with Denamarin (84% versus 68%). Denamarin administration should be considered in all dogs with cancer that are prescribed CCNU with or without corticosteroids. Although additional studies are

needed, administration of this SAMe and silybin product is likely to limit hepatocellular damage seen with CCNU and increase the likelihood a dog can complete a course of chemotherapy.

Prebiotics, Probiotics, and Symbiotics

Prebiotics refer to starches and fibers that are resistant to digestion that select for enteric bacterial that can utilize them as substrates. Probiotics refer to live microbial cultures, typically *Lactobacillus* spp and *Enterococcus* spp. They have been recommended for 'normalizing' the gastrointestinal tract in patients with diarrhea, inflammatory bowel disease, and food allergies, but have also been recommended for use with atopic dermatitis, recurrent bacterial urinary tract infections, and chronic antimicrobial administration. Four citations were found through PubMed. In one study of dogs with tylosin-responsive diarrhea, *Lactobacillus* did not prevent relapse. In another study, pro-biotic treatment was associated with improvement in canine inflammatory bowel disease scoring when compared with placebo. Recently, a probiotic has become available for use in dogs with chronic renal failure and marketed as 'enteric dialysis'. No controlled data is available for this product, but the data that is available shows a slight reduction in blood urea nitrogen and creatinine. This concept is similar to 'nitrogen repartitioning' utilizing dietary prebiotics. This is not truly dialysis as it does not appear to affect electrolyte, acid-base, or mineral balance as hemodialysis or peritoneal dialysis does. More of a concern is a report from Consumerlab.com, which showed that 44% of probiotic supplements contained fewer viable organisms than claimed or generally known to be effective. Only 1 of 3 veterinary products contained a large enough dose of viable organisms.

Probiotics - as a general rule: "more is better" - more bugs of more types in more numbers. VSL#3 has 450 billion organisms of 8 strains (http://vsl3.com/), Culturelle has 10 billion organisms of 1 strain, Proviable has 5 billion organisms of 7 strains, ProstoraMaxx has 100 million organisms of 1 strain, and Fortiflora has 10 million organisms of 1 strain.

NUTRICEUTICALS FOR URINARY DISEASE (AND OTHER USES)

Rhemania

Rehmannia is a genus of six species of flowering plants in the order Lamiales, endemic to China. Sometimes known as Chinese Foxglove due to its superficial resemblance to the genus *Digitalis*, the species of *Rehmannia* are perennial herbs. The plants have large flowers and are grown as ornamental garden plants in Europe and North America, and are used medicinally in Asia. *R. glutinosa* is used as a medicinal herb for anemia, dizziness constipation, hypertension, and as a diuretic, *Rhemannia* contains the vitamins A, B, C, and D, as well as other useful compounds. An extract of *Rhemania* is marketed for use with chronic kidney disease; however, no data are available to support its use and one study in cats did not show a benefit.

NUTRICEUTICALS FOR CANCER

Coriolus versicolor Mushroom Extract

The *Coriolus versicolor* mushroom, commonly referred to as cloud mushroom, turkey tail, or Yunzhi mushroom in China, contains polysaccharopeptide (PSP). PSP has been shown to cause cell cycle arrest specifically at the G1/S checkpoint with alterations in expression of apoptogenic and extracellular signaling proteins. The net result is a reduction in proliferation and an increase in apoptosis in cancer cells. A randomized, double-blind, multi-dose pilot study examined the effects of I'm-Yunity, a proprietary fractionation of *Coriolus versicolor* mushroom extract (Integrated Chinese Medicine Holdings, Ltd., Hong Kong, China), in 15 dogs with a histopathologic diagnosis of splenic hemangiosarcoma following splenectomy. Median time to development or progression of abdominal metastases was significantly delayed in dogs receiving 100 mg/kg/day I'm-Yunity (112 days; range 30–308 days) compared to dogs receiving 25 mg/kg/day (30 days; range 16–126 days; $P = 0.046$), but was not significantly different than in dogs receiving 50 mg/kg/day; however, there was no placebo group. There were no adverse events reported.

Maitake Mushroom (*Grifola frondosa*) Extract

Another study used a standardized formulation of maitake (*Grifola frondosa*) mushroom extract (Maitake PETfraction, PureFormulas, Medley, FL, USA) in 15 dogs with intermediate and high grade lymphoma. Although the extract was well tolerated and induced no negative effects, there was also no decrease greater than 50% (objective response) in lymph node size in 13/15 dogs.

Evaluating Nutraceuticals

Since there is no regulatory body for manufacturing of nutraceuticals, it is difficult to assess quality. Drugs are regulated by the FDA and must meet specific manufacturing standards; however, nutraceuticals are not considered drugs. Often, nutraceuticals are mislabeled, may contain impurities, may have variable quantities of active ingredients, or the active ingredient may not be bioavailable. Some guidelines for selecting products **likely to be** of better quality include (VIN: Evaluating Nutraceuticals and Supplements by Rischnow and Wynn):

1. Price. Cheaper compounds are less likely to be of high quality. This has been the general observation with chondroitin sulfate.
2. Lot number and Expiration Date.
3. Monograph within the US Pharmacopeia, documenting accuracy of ingredient labeling. There is a USP Dietary Supplement Verification Program page (www.usp.org/dietary-supplements/overview), which provides a list of suppliers that have voluntarily submitted their products for USP verification (www.usp.org/usp-verification-services and approval and information on compounding (www.usp.org/usp-healthcare-professionals/compounding/veterinary-compounding-monographs). However, this does not mean that products not verified by USP DSVP are of poor quality.
4. Claims of safety or efficacy. If a nutraceutical claims a medical benefit on the label, there should be a New Animal Drug Application (NADA) number accompanying the product. While this is "mandated" by law, it is often ignored. A NADA tends to suggest higher quality, because the manufacturer has bothered to abide by FDA regulations for drug manufacture.
5. Ingredient list. All ingredients should be listed by order of magnitude based on weight.
6. Good instructions for use.
7. Scientific evidence supporting manufacturer's claims. Some manufacturers have begun providing data for their specific products through independent scientific studies. These studies should ideally be peer-reviewed and published. Importantly, they should be **clinical studies**, not *in vitro* studies. There are institutes, affiliated with universities and medical schools, who are beginning to investigate nutraceutical claims scientifically.
8. Testimonials in place of valid research. Many companies provide testimonials from "satisfied clients". These should be ignored, and companies that promote these instead of scientific research supporting their claims, should be viewed skeptically.
9. Membership in National Animal Supplement Council (www.nasc.cc). This industry group has a close relationship with FDA and strict guidelines for member companies regarding quality control and adverse event recording. Member companies are likely to have better quality products.

Evaluating safety and efficacy of a product is difficult. Ask manufacturers about specific formulations. The best measure is results of controlled clinical studies. Dr Andrea Fascetti of UC Davis provides some useful guidelines that a clinician should ask prior to prescribing a nutraceutical:

1. "Does the product do what it claims to do?" "What studies have been done to prove this, or are testimonials the only proof?"
2. "Does the product contain what it claims it does, and if so, is the product bioavailable?"
3. "If studies have been conducted on the compound, were they *in vivo* or *in vitro*?"
4. "Were the studies done in the target species?"
5. "Did the studies employ the same dose as is contained in the product?"
6. "Were the studies well-controlled?"
7. "Were the studies published in a peer-reviewed journal or similarly reputable source?"

8. "What are the active ingredients in products containing multiple substances, and what is the potential they may interact in a negative manner?"
9. "What other medications is my patient receiving, and how might the nutraceutical in question interact with them?"
10. "What work has been done to verify the safety at the dosage of intended use?"
11. "Has a margin of safety (the difference between effective dose and maximum safe dose) been established?"

Several websites exist that may help a clinician investigate specific nutraceuticals: Quackwatch (www.quackwatch.com). The American Botanical Council (http://abc.herbalgram.org); The NIH National Center for Complementary and Integrative Health (https://nccih.nih.gov); Tufts Medical Center - Center for Complementary and Integrative Medicine (www.tuftsmedicalcenter.org/patient-care-services/Departments-and-Services/Rheumatology/Research-Clinical-Trials/Center-for-Complementary-and-Integrative-Medicine.aspx) Consumer Labs (www.consumerlab.com); and the American College of Veterinary Nutrition (www.acvn.org).