

**NATURAL TOOLS** Discussing the complementary role of herbs and dietary supplements with clients provides an opportunity for the veterinarian to strengthen the veterinarian-client relationship.

## NUTRITION NOTES

# Supplements for Small Animal Cancer Patients

Donna Raditic, DVM, DACVN, CVA, and Laura Gaylord, DVM, DACVN  
Veterinary Nutritional Consultations, Inc, Hollister, N.C.

This article completes a 2-part series covering nutrition issues for small animal cancer patients. For information specifically addressing diet considerations for cancer patients, see the [January/February](#) issue or visit [todaysveterinarypractice.com](http://todaysveterinarypractice.com).

In human medicine, a recent review reported that in the United States, 52% of healthy adults use herbs and dietary supplements (HDS).<sup>1</sup> Surveys of human cancer survivors report that 70% to 81% use HDS but that up to 68% of physicians were unaware of their cancer patients' supplement use.<sup>2,3</sup>

In veterinary medicine, HDS are also used for cancer patients. One study reported that among 254 owners of pets with cancer, 65% gave the pet some type of complementary medicine, most commonly dietary supplements, and 57% did not discuss their use of supplements or other complementary medicines with their veterinarian. Reasons for providing complementary therapy and HDS were to improve their pet's wellbeing and immune function and reduce pain; only 9% reported pursuing complementary therapies to cure their pet's cancer.<sup>4</sup> A survey of 213 owners of healthy dogs and 132 owners of dogs with cancer found that supplement use was more common among cancer patient owners.<sup>5</sup> The most frequently used were cannabidiol products, mushroom extracts, or turmeric/curcumin.

For human healthcare professionals, a list of leading supplements that are considered relatively safe and have the "best suggestion of benefit" has been published.<sup>1</sup> Before veterinarians recommend use of HDS for cancer patients, they need to understand the products' mode of action or specific benefits. Some HDS can increase or decrease cancer treatment effects, and others may mitigate treatment side effects. Some HDS can be used to help manage other concurrent disease processes and/or support the patient's overall wellbeing and quality of life. Use of all treatments including HDS should be evidence-based, which means considering client values (i.e., perspectives and needs). HDS can be safely integrated into the care and management of cancer patients with the concept of *primum non nocere* (first do no harm), perhaps providing some benefits while honoring the client's values.

Given the vast array of pet supplements available in today's market ([TABLE 1](#)), selecting and recommending safe supplements can be challenging. The following 3 criteria can be used as guidelines for identifying safe, appropriate HDS for cancer patients: supplements are made by manufacturers that you have reasons to trust,



safety and efficacy are supported by research, and supplements carry the National Animal Supplement Council (NASC) Quality Seal. The NASC seal indicates that the manufacturing company has passed an independent facility audit every 2 years and demonstrates ongoing compliance by implementing quality control standards, reporting adverse events, complying with all labeling guidelines, and randomly testing products.

The authors describe common HDS that, according to their clinical experience, are relatively safe and may be beneficial for pets. Products to consider for veterinary cancer patients include mushroom extracts, turmeric/curcumin, milk thistle, probiotics, fish oils, and hemp/cannabinoids.

## MUSHROOM EXTRACTS

Mushroom extracts contain  $\beta$ -D-glucans, which are bioactive polysaccharides of high molecular weight. These complex branched-chain polysaccharides promote immunomodulating activity by activating macrophages, monocytes, natural killer cells, dendritic

cells, and lymphocytes. They have been shown to have antitumor effects in melanoma and lung, breast, cervical, and prostate cancers.<sup>6</sup> One of the most studied mushrooms is the turkey tail mushroom (*Coriolus versicolor*); its extracts, such as polysaccharide K (PSK) and polysaccharopeptide (PSP), are used to treat human cancer patients. Numerous peer-reviewed publications on their antitumor effects describe in vitro and in vivo animal studies as well as clinical cancer trials among humans with gastrointestinal, breast, and lung cancers.<sup>7,8</sup> In a small multidose pilot study, 15 dogs with splenic hemangiosarcoma that were given I'm-Yunity (HYY, [hyy.com.hk](http://hyy.com.hk)) at 100 mg/kg/day experienced a significant delay of median time to development or progression of abdominal metastases.<sup>9</sup> A larger randomized clinical controlled trial comparing this turkey tail extract with doxorubicin in dogs with splenic hemangiosarcoma was completed in spring 2019 but has not yet been published.<sup>10</sup> In another yet-unpublished clinical trial, dogs with stage II hemangiosarcoma were given a turkey tail granular extract along with standardized bupleurum-based herbal formula, vitamin D, and Yunnan Baiyao.<sup>11</sup>

**TABLE 1 Common Herbal and Dietary Supplements**

HERB OR SUPPLEMENT	PROPOSED PROPERTIES/BENEFITS	INDICATIONS	PRODUCT EXAMPLES (MANUFACTURER)
<b>Mushroom extract</b>	<ul style="list-style-type: none"> <li>Immune support</li> <li>Maintain quality of life</li> </ul>	<ul style="list-style-type: none"> <li>Hemangiosarcoma or other sarcomas</li> <li>Lymphoma or other immune cell neoplasia</li> </ul>	<ul style="list-style-type: none"> <li>I'm-Yunity (HYY)</li> <li>Maitake PETfraction (Mushroom Wisdom)</li> <li>Mycogen (Pet Health Solutions)</li> <li>Rx Coriolus Forte (Rx Vitamins for Pets)</li> </ul>
<b>Turmeric/curcumin</b>	<ul style="list-style-type: none"> <li>Immune support</li> <li>Anti-inflammatory</li> <li>Antioxidant</li> <li>Hepato-protective</li> </ul>	<ul style="list-style-type: none"> <li>All cancer types</li> <li>Concurrent osteoarthritis</li> <li>Concurrent hepatic dysfunction</li> <li>Hepatotoxic chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Turmeric (NHV)</li> <li>RxCurcuWIN (Rx Vitamins for Pets)</li> <li>Hepagen (ThorneVet)</li> </ul>
<b>Milk thistle products</b>	<ul style="list-style-type: none"> <li>Hepato-protective</li> <li>Renal-protective</li> <li>Antioxidant</li> </ul>	<ul style="list-style-type: none"> <li>Concurrent hepatic dysfunction</li> <li>Concurrent renal dysfunction</li> <li>Hepatotoxic chemotherapy</li> <li>Nephrotoxic chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Denamarin (Nutramax Laboratories, Inc.)</li> <li>Milk Thistle Liver Support (Herbsmith, Inc.)</li> <li>Milk Thistle for Dogs (NHV)</li> <li>Animal Essentials Milk Thistle (Animal Essentials)</li> </ul>
<b>Probiotics</b>	<ul style="list-style-type: none"> <li>Immune support</li> <li>Gastrointestinal function support</li> </ul>	<ul style="list-style-type: none"> <li>Concurrent gastrointestinal disease</li> <li>Treatment-induced gastrointestinal dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>Visbiome Vet (ExeGi Pharma)</li> <li>FortiFlora Canine Probiotic Supplement (Nestle Purina PetCare Company)</li> <li>Lactoquil Digestive Health Probiotic (Elanco)</li> <li>Vetri Mega Probiotic (VetriScience)</li> </ul>
<b>Fish oil products</b>	<ul style="list-style-type: none"> <li>Anti-inflammatory</li> </ul>	<ul style="list-style-type: none"> <li>All cancer types</li> <li>Concurrent osteoarthritis</li> <li>Radiation treatments</li> </ul>	<ul style="list-style-type: none"> <li>Free Form Omega-3 Fish Oil (Elanco)</li> <li>Triglyceride OMEGA (Vetoquinol)</li> <li>EicosaCaps (Dechra)</li> <li>Omega-3 Pet (Nordic Naturals)</li> </ul>
<b>Hemp/cannabinoid products</b>	<ul style="list-style-type: none"> <li>Pain management</li> <li>Quality of life</li> </ul>	<ul style="list-style-type: none"> <li>Concurrent osteoarthritis</li> <li>Chronic pain</li> </ul>	<ul style="list-style-type: none"> <li>Ellevet Hemp CBD+CBDA Oil and Chews (ElleVet Sciences)</li> <li>HempRx (Rx Vitamins for Pets)</li> </ul>

Use of Maitake mushrooms (*Grifola frondosa*) as a standardized formulation, Maitake PETfraction (Mushroom Wisdom Inc., [mushroomwisdom.com](http://mushroomwisdom.com)), was evaluated in 15 dogs with intermediate and high-grade lymphoma.<sup>12</sup> Although the supplement was well tolerated with no negative effects, no lymph node size decrease greater than 50% was reported.<sup>12</sup> Another study in which the supplement K-9 Immunity and its adjunct K-9 Transfer Factor (K9 Medicinals, [k9medicinals.com](http://k9medicinals.com)) were given concurrently with chemotherapy in dogs with various types of cancer showed a reduction in the common side effect of neutropenia while maintaining quality of life.<sup>13</sup>

These studies in dogs with cancer, numerous other animal studies, and human trials indicate that use of mushroom extracts should be considered relatively safe and may have some benefits for the veterinary cancer patient.

## TURMERIC/CURCUMIN

Curcumin (diferuloylmethane) is an active constituent of the spice turmeric (*Curcuma longa*). It influences many cell-signaling pathways involved in tumor initiation and proliferation.<sup>14</sup> Studies also demonstrate curcumin's anti-inflammatory effects as a cyclooxygenase 2 (COX-2) inhibitor. Turmeric and curcumin are nontoxic and have been shown to be safe for oral use in humans and animals;<sup>15</sup> curcumin is designated as a GRAS (generally recognized as safe) substance for humans. GRAS is a U.S. Food and Drug Administration (FDA) designation that a substance added to food is considered safe by experts and so is exempted from the usual Federal Food, Drug, and Cosmetic Act food additive tolerance requirements. Oral administration of turmeric and curcumin is well tolerated; the only reported concern is gastrointestinal upset in some humans and animals when given at extremely high doses.<sup>15,16</sup>

Turmeric is a common ingredient in many pet joint supplements, which may benefit dogs with cancer and concurrent osteoarthritis.

## MILK THISTLE (*SILYBUM MARIANUM*)

Silybins are among the active ingredients in the milk thistle herb. Silybin A and B are ingredients in the hepato-protectant pet supplement Denamarin (Nutramax Laboratories, [nutramaxlabs.com](http://nutramaxlabs.com)). A study

of 50 dogs with cancer showed that Denamarin has protective effects on CCNU (lomustine)-induced hepatotoxicity; alanine aminotransferase (ALT) levels increased by 84% in the dogs receiving CCNU alone compared with only 68% in dogs receiving CCNU plus Denamarin.<sup>17,18</sup> Other studies have found that this very safe herb also has renal protectant properties.<sup>19,20</sup>

Because many chemotherapeutics negatively affect liver and kidney function, a milk thistle supplement may benefit veterinary cancer patients receiving chemotherapy. Furthermore, these patients may already have concurrent hepatopathy or renal compromise, making a milk thistle supplement a logical recommendation.

## PROBIOTICS

The World Health Organization defines probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.”<sup>21</sup> Research has demonstrated the role of probiotics in modulating gut microbiota, but they may also inhibit tumor progression, produce anticancer compounds, and modulate the host immune response.<sup>22-24</sup> Studies of probiotic use in dogs and cats have primarily focused on gastrointestinal diseases, but studies among humans have found that probiotics have positive effects in oncology patients receiving treatments.<sup>25,26</sup>

Because many veterinary cancer patients experience gastrointestinal dysfunction either primarily or secondarily to their cancer and/or cancer treatment, use of probiotics for these patients seems logical.

## FISH OILS

Fish oils are a potent source of omega-3 (n-3) fatty acids or n-3 polyunsaturated fatty acids, most notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). For inflammatory states resulting from various diseases in dogs, EPA plus DHA at a dose range of 50 to 150 mg/kg/day has been recommended.<sup>27</sup> A clinical trial that compared the effects of n-3 fatty acids with soybean oil in 32 dogs receiving doxorubicin for stage III lymphoma found that the dogs receiving n-3 fatty acids had increased levels of DHA, longer disease-free intervals, and longer survival times.<sup>28</sup> Other studies of n-3 fatty acids in dogs, humans, and rodent cancer models have shown similar benefits and/or reduction of detrimental inflammation associated with cancer and/or cancer treatments.<sup>29-31</sup>

Recommending n-3 supplements because of their anti-inflammatory properties for the canine cancer patient is safe and appropriate. Note, however, that doses of n-3 supplements may need to be modified for patients that may not tolerate higher dietary fat levels (e.g., those with concurrent pancreatitis, hyperlipidemia, or protein-losing enteropathy).

## HEMP/CANNABINOID PRODUCTS

Use of cannabis products to decrease pain and improve quality of life in veterinary cancer patients is gaining interest. Cannabis refers to the plant *Cannabis sativa*, of which there are thousands of varieties with different types and amounts of cannabinoids and other constituents (e.g., terpenes). The 2 main cannabinoids in the cannabis plant are cannabidiol (CBD) and  $\Delta$ -9-tetrahydrocannabinol (THC). Hemp and marijuana are legal terms that refer to cannabis plant varieties with very different compositions of THC. Hemp refers to cannabis plant varieties with very low levels of THC (less than 0.3% on a dry weight basis), whereas marijuana refers to cannabis plant varieties with higher levels of THC (greater than 0.3%). THC is the active ingredient associated with marijuana's intoxicating ("high") effect. The active ingredients in *C sativa* have therapeutic efficacy in the control of pain in humans and animals, although studies in veterinary patients are limited.<sup>32</sup>

The FDA acknowledges the public interest in hemp/cannabinoid products and has an internal CBD working group committed to evidence-based decision making and ensuring the health and safety of humans and animals (including pets). Currently, the FDA states that cannabis and cannabis derivatives such as CBD may not be added to food or dietary supplements. The FDA position that cannabis and cannabis derivatives are not approved or appropriate for use in animal food/feed is acknowledged and supported by state regulators, the Association of Animal Feed Control Officials, and the NASC. Because pet supplements do not have a clear regulatory definition, the NASC does allow companies to use cannabis and/or CBD or hemp in pet supplement products that are not food/feed and are used for non-nutritional purposes, provided the company acts responsibly. Because of the complex and changing regulatory oversight, veterinarians should contact and follow their own state board regulations regarding hemp/cannabinoid pet supplements and, at the very least, be sure which hemp/cannabis products have NASC approval.

A 2018 study of use of a CBD oil product in 16 dogs with osteoarthritis reported improved pain scores and increased comfort and activity in the home environment. Evaluation of pharmacokinetics in the same study suggested that CBD at 2 mg/kg q12h can help increase comfort and activity in dogs with osteoarthritis.<sup>33</sup> A single-dose pharmacokinetic study along with 12-week dosing of 2 mg/kg PO q12h in dogs and cats reported no changes in physical examination findings, minimal changes in bloodwork parameters (one feline patient had a persistent rise in ALT), and some licking and head shaking by cats.<sup>34</sup> Another study tested 29 pet supplements that use low-THC *C sativa* extracts in their production for CBD, THC, and other cannabinoids; all products were found to contain less than the federal (FDA) limit of 0.3% THC and variable amounts of CBD (0 to 88 mg/mL, or mg/g).<sup>35</sup> According to current FDA regulations for nonmedication, nondietary supplements, 18 of these 29 supplements were appropriately labeled.<sup>35</sup>

Veterinarians wanting to recommend CBD-rich *C sativa* products should be aware of the range of CBD concentrations in these products. Also recommended is obtaining a Certificate of Analysis from the manufacturer to determine appropriate use and dosing for pets.<sup>35</sup>

## SUMMARY

Veterinarians face multiple questions and challenges from clients whose pets have cancer. Veterinarians need to rely on scientific evidence yet cannot overlook the client's perspective. Human cancer patients reportedly use nutrition, supplements, and natural products to empower themselves, attempt to take control of their health, and increase quality of life. Given the humanization of pets today, it is logical to respect these same emotions from clients dealing with cancer in their pet. Clients are usually highly motivated to participate in the healthcare of their pet with cancer and often look for nutritional and supplement recommendations to maintain quality of life and improve outcomes. The veterinarian and healthcare team are expected to know about safe and appropriate HDS and address their use. Discussing the complementary role of HDS with clients provides an opportunity for the veterinarian to strengthen the veterinary healthcare team/client/patient bond. Veterinarians should be comfortable recommending HDS products that are first and foremost safe but that are also appropriate for the patient with cancer. In the authors' clinical experience,

clients appreciate veterinary guidance and the logical integration of appropriate HDS supplements with conventional therapies.

## References

- Frenkel M, Abrams DI, Ladas EJ, et al. Integrating dietary supplements into cancer care. *Integr Cancer Ther* 2013;12(5):369-384.
- Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. *J Clin Oncol* 2008;26(4):665-673.
- Du M, Luo H, Blumberg JB, et al. Dietary supplement use among adult cancer survivors in the United States. *J Nutr* 2020;150(6):1499-1508.
- Lana SE, Kogan LR, Crump KA, et al. The use of complementary and alternative therapies in dogs and cats with cancer. *JAAHA* 2006;42(5):361-365.
- Bianco AV, Abood S, Mutsaers A, et al. Unconventional diets and nutritional supplements are more common in dogs with cancer compared to healthy dogs: an online global survey of 345 dog owners. *Vet Comp Oncol* 2020;18(4):706-717.
- Wasser SP. Medicinal mushrooms in human clinical studies. part i. anticancer, oncoimmunological, and immunomodulatory activities: a review. *Int J Med Mushrooms* 2017;19(4):279-317.
- Raditic D, Bartges JW. Evidence-based integrative medicine in clinical veterinary oncology. *Vet Clin North Am Small Anim Pract* 2014;44(5):831-853.
- Patel S, Goyal A. Recent developments in mushrooms as anti-cancer therapeutics: a review. *J Biotech* 2012;2(1):1-15.
- Brown DC, Reetz J. Single agent polysaccharopeptide delays metastases and improves survival in naturally occurring hemangiosarcoma. *Evid Based Complement Alternat Med* 2012;2012:384301.
- Baillie KU. Compound derived from a mushroom lengthens survival time in dogs with cancer, Penn Vet study finds. [penntoday.upenn.edu/news/compound-derived-mushroom-lengthens-survival-time-dogs-cancer-penn-vet-study-finds](http://penntoday.upenn.edu/news/compound-derived-mushroom-lengthens-survival-time-dogs-cancer-penn-vet-study-finds). Accessed January 2021.
- Bannink E. Clinical trial announcement. Innovative Veterinary Care 2019 (May 16, 2019). [ivcjournal.com/traditional-chinese-medicine-herbal-therapy-splenic-hemangiosarcoma](http://ivcjournal.com/traditional-chinese-medicine-herbal-therapy-splenic-hemangiosarcoma). Accessed January 2021.
- Griessmayr PC, Gauthier M, Barber LG, Cotter SM. Mushroom-derived maitake PETfraction as single agent for the treatment of lymphoma in dogs. *J Vet Intern Med* 2007;21(6):1409-1412.
- Holliday JC, Gianotti BM, Cleaver MP, et al. Preclinical evaluation of concurrent medicinal mushroom-based immune-enhancement supplementation in dogs undergoing chemotherapy for various cancers. *Int J Med Mushrooms* 2009;11(2):167-184.
- Shehzad A, Lee J, Lee YS. Curcumin in various cancers. *Biofactors* 2013;39(1):56-68.
- Soleimani V, Sahebkar A, Hosseinzadeh H. Turmeric (*Curcuma longa*) and its major constituent (curcumin) as nontoxic and safe substances: review. *Phytother Res* 2018;32(6):985-995.
- Shehzad A, Lee YS. Molecular mechanisms of curcumin action: signal transduction. *Biofactors* 2013;39(1):27-36.
- Skorupski KA, Hammond GM, Irish AM, et al. Prospective randomized clinical trial assessing the efficacy of Denamarin for prevention of CCNU-induced hepatopathy in tumor-bearing dogs. *J Vet Intern Med* 2011;25(4):838-845.
- Bijak M. Silybin, a major bioactive component of milk thistle (*Silybum marianum* L. Gaertn.)—chemistry, bioavailability, and metabolism. *Molecules* 2017;22(11):1942.
- Karimi G, Ramezani M, Tahoonian Z. Cisplatin nephrotoxicity and protection by milk thistle extract in rats. *Evid Based Complement Alternat Med* 2005;2(3):383-386.
- Sedighifard Z, Roghani F, Bidram P, et al. Silymarin for the prevention of contrast-induced nephropathy: a placebo-controlled clinical trial. *Int J Prev Med* 2016;7:23.
- Hill C, Guarner F, Reid G, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014;11:506-514.
- So SS, Wan ML, El-Nezami H. Probiotics-mediated suppression of cancer. *Curr Opin Oncol* 2017;29(1):62-72.
- Kerry RG, Patra JK, Gouda S, et al. Benefaction of probiotics for human health: a review. *J Food Drug Anal* 2018;26(3):927-939.
- Yu AQ, Li L. The potential role of probiotics in cancer prevention and treatment. *Nutr Cancer* 2016;68(4):535-444.
- Gopalakrishnan V, Helmink BA, Spencer CN, et al. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. *Cancer Cell* 2018;33(4):570-580.
- Deng P, Swanson KS. Gut microbiota of humans, dogs and cats: current knowledge and future opportunities and challenges. *Br J Nutr* 2015;113 Suppl:S6-17.
- Bauer JE. Therapeutic use of fish oils in companion animals. *JAVMA* 2011;239(11):1441-1451.
- Ogilvie GK, Fettman MJ, Mallinckrodt CH, et al. Effect of fish oil, arginine, and doxorubicin chemotherapy on remission and survival time for dogs with lymphoma: a double-blind, randomized placebo-controlled study. *Cancer* 2000;88(8):1916-1928.
- Seidel A, Gueck T, Fuhrmann H. The influence of long-chain polyunsaturated fatty acids on total lipid fatty acid composition of a canine mastocytoma cell line. *J Vet Med A Physiol Pathol Clin Med* 2005;52(5):219-224.
- Freitas RDS, Campos MM. Protective effects of omega-3 fatty acids in cancer-related complications. *Nutrients* 2019;11(5):945.
- Siddiqui RA, Harvey KA, Zaloga GP, Stillwell W. Modulation of lipid rafts by omega-3 fatty acids in inflammation and cancer: implications for use of lipids during nutrition support. *Nutr Clin Pract* 2007;22(1):74-88.
- Barbagallo S, Finocchiaro S, Ahmadi M. Veterinary medical use of cannabis, cannabinoid receptors and endocannabinoids system in mammals. *Lucrari Stiintifice - Universitatea de Stiinte Agricole a Banatului Timisoara, Medicina Veterinara* 2019;52(1):5-13.
- Gamble LJ, Boesch JM, Frye CW, et al. Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. *Front Vet Sci* 2018;5:165.
- Deabold KA, Schwark WS, Wolf L, Wakshlag JJ. Single-dose pharmacokinetics and preliminary safety assessment with use of CBD-rich hemp nutraceutical in healthy dogs and cats. *Animals (Basel)* 2019;9(10):832.
- Wakshlag JJ, Cital S, Eaton SJ, et al. Terpene, and heavy metal analysis of 29 over-the-counter commercial veterinary hemp supplements. *Vet Med (Auckl)* 2020;114:5-55.

### Donna Raditic

Dr. Raditic is a former professor at the University of Tennessee College of Veterinary Medicine. Currently, she is an independent consultant member of Veterinary Nutritional Consultations, Inc., the East Coast Think Tank, which offers independent information and consulting on companion animal nutrition and supplements. She offers unique perspectives on the role of clinical nutrition, supplements, and integrative veterinary care for companion animals.



### Laura Gaylord

Dr. Gaylord has been a general practitioner in North Carolina for more than 20 years. She is currently an independent consultant member of Veterinary Nutritional Consultations, Inc., the East Coast Think Tank, with Dr. Raditic. Combining her clinical experiences with “out of the box” thinking, she consults on pet nutrition and supplements for general practitioners and their clients, as well as the pet-vested industry.

