Evidence-based Integrative Medicine in Clinical Veterinary Oncology

Donna M. Raditic, DVM, CVA*, Joseph W. Bartges, DVM, PhD

KEYWORDS

• Complementary and alternative medicine • Integrative medicine
• Veterinary oncology • Cancer • Neoplasia • Dietary supplements • Herbs
• Nutraceutical

KEY POINTS

- There is a growing demand for use of integrative medicine in veterinary clinical oncology.
- Evidence-based research on using integrative medicine in veterinary clinical oncology is scarce.
- Translational research with animal models of human cancers is an opportunity to expand the knowledge of the etiopathogenesis of neoplasia and identify treatments.
- Metabolomics research may provide the evidence-based research needed to accelerate the use of complementary and alternative medicine in both human and veterinary oncology.

Integrative medicine (IM) is the use of complementary and alternative medicine (CAM) with conventional Western medicine systems. CAM therapies include herbs, supplements, acupuncture, massage, and others that are rational and supported by evidence to alleviate physical and emotional symptoms, improve quality of life (QOL), and possibly improve adherence to oncology treatment regimens. Demand for IM is growing, and veterinarians are being challenged to know more about these therapies.[1,2]

Herbs and dietary supplements (HDS) are the most accessible form of CAM. Reportedly, more than half of the human population used HDS between 2003 and 2006. In 2010, US herbal supplement sales exceeded $5.2 billion.[3] Between 20% and 55% of human patients with cancer use HDS. Specifically, 67% to 87% of women with breast cancer and those 9 years after diagnosis use supplements. One study reported that 67% of clients gave their pets with cancer HDS, indicating commonplace use.[4]

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Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, 2407 River Drive, Knoxville, TN 37996, USA
* Corresponding author.
E-mail address: draditic@utk.edu

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In treating a patient with cancer being given supplements, veterinarians face multiple questions and challenges, the most important being safety and efficacy. Veterinarians must rely on scientific evidence but cannot overlook the client's perspective. Reportedly, human oncology patients use natural products to empower themselves, attempt to take control of their health, and increase QOL.[3] Considering the strength of the human-animal bond, logically pet owners would apply these same emotions.[5] Owners use supplements, herbs, massage, and acupuncture in their own health care, so they expect veterinarians to have a basic understanding of CAM, especially with respect to cancer, chronic illnesses, and geriatrics.

Knowledgeable patients value physicians who embrace them as empowered participants in making their own health care decisions. The health care provider in this shifted perspective is an informed intermediary, an expert guide, and a consultant to the patient. The Society of Integrative Oncology in 2009 outlined guidelines for IM as part of cancer care. The Clinical Practice Committee outlined best recommendations for curcumin, glutamine, Vitamin D, maitake mushrooms, fish oils, green tea, milk thistle, Astragalus, melatonin, and probiotics.[3]

If a veterinarian is not responsive and knowledgeable about CAM, owners will likely seek advice from friends, nonprofessional literature, and the Internet, which provide ample but possibly incorrect information. In 2005, 60% of veterinarians reported that they needed skills or knowledge related to CAM on a weekly or monthly basis and 7% indicated situations arose daily. CAM is incorporated less into veterinary curricula than in medical schools.[6]

Evidence-based research on CAM in an IM plan in veterinary clinical oncology is scarce, which is expected because large-scale research funding is typically provided for projects with potential for profits, such as with new, patented drugs. Still, value exists in assessing current literature and exploring IM that either has potential or is already based on evidence for use in veterinary oncology with respect to growth of translational research and the "One Health" movement.

Animal models of human cancers are an opportunity to help both veterinary and human patients by expanding the knowledge of the pathogenesis of neoplasia and identifying specific treatments. Pets live in the same environments as humans and eat similar foods, thus are exposed to similar risk factors; therefore, the etiopathogenesis of canine and feline tumors is likely similar to that of human tumors. For example, breast cancer is the most common malignancy in women, and the mammary gland is a common site for tumor development in bitches.[7]

Veterinary pilot studies can justify investment of sizable resources required to complete larger trials, especially when positive results are documented in an animal model. In preclinical studies of cancer therapeutics, important information could be acquired for new and innovative therapies. Advantages are that dogs develop cancer about twice as frequently as humans, and the presentation, histology, and biology of many canine cancers closely parallel human cancers. In addition, body size of dogs simplifies biologic sampling, whereas shorter overall lifespan allows for spontaneous development and course of disease within a time frame reasonable for data collection.[8]

Cancer is an important disease in dogs and accounts for 27% of all deaths in purebred dogs in the United Kingdom. Without reliable historical tumor registries, it is difficult to know whether prevalence of cancer in dogs is increasing. However, animals are living longer as a result of improvements in health care, and cancer is generally a disease of older age.[7] Also, advances in veterinary medicine, particularly diagnostics, and higher owner expectations are likely to result in increased diagnosis. Focus on QOL comes to the forefront of a veterinary treatment plan because the patient has a shorter lifespan than a human, and economics of treatment is different. With a

diagnosis of cancer comes an opportunity to explore an IM approach in veterinary clinical oncology, as illustrated by the pilot trial using *Coriolus versicolor* mushroom extract in treatment of canine hemangiosarcoma.[8]

Quantitatively measuring the dynamic, multiparametric metabolic responses of living systems to pathophysiological stimuli or genetic modification (metabolomics) may be an avenue to develop evidence-based research for the use of IM. Recent metabolomic studies have demonstrated significant potential of IM in areas such as responses to environmental stress, toxicology, nutrition, global effects of genetic manipulation, cancer, diabetes, disease diagnosis, and natural product discovery. A major benefit of metabolomics is that profiling can usually be achieved by noninvasively examining urine or plasma samples with proton nuclear magnetic resonance (NMR) spectroscopy, high-power liquid chromatography, and mass spectroscopy for biomarkers that could detect early-stage disease, identify residual disease postsurgery, and help to monitor response and detect early toxicity.[9] Interestingly, one of the goals of metabolomics studies is identifying discrete patterns and specific treatments in oncology patients, which parallels IM's emphasis on the individual, known as "patient-centered care." Combining translational medicine and metabolomics research may spawn rapid development in veterinary oncology.

Ideally, an integrative approach to veterinary clinical oncology should target many physiologic and biochemical tumor pathways while minimizing normal tissue toxicity and supporting overall QOL. The oncologist should first *primum non nocere*, or do no harm, while weighing risks and benefits of conventional treatment. Integrating CAM must be done *non nocere* with consideration of evidence of available research.

Because of the lack of formal education regarding IM in veterinary medical curricula and sparse research, the authors consulted with experienced veterinarians who use CAM to determine what is being used clinically in integrative veterinary oncology (Erin Bannink, DVM, DACVIM [oncology], Bloomfield Hills, MI, personal communication, 2013; and Steve Marsden, DVM, ND, MSOM, L.Ac, Dipl. CH, RH [AGH], Edmonton, Alberta, Canada, personal communication, 2013).[10] The evidence base for the use of relevant HDS was assessed via a literature search for uses of HDS in the dog/cat, in vitro using dog/cat cells, and then in other species, including humans or in vitro cell lines. No meta-analysis and few randomized controlled clinical trials (RCCT) using supplements in veterinary oncology were found. Reports on use of HDS in feline oncology and feline cells are minimal.

HERBS/BOTANICS EVALUATED IN DOGS OR IN VITRO CANINE CELLS

Few herbs or botanic extracts have been evaluated in RCCTs in dogs and canine cancer cells. The *C versicolor* mushroom, commonly referred to as cloud mushroom, turkey tail, or Yunzhi mushroom in China, contains polysaccharopeptide (PSP), which causes cell-cycle arrest at the G_1/S checkpoint with alterations in apoptogenic and extracellular signaling proteins. The net result is a reduction in proliferation and an increase in apoptosis in cancer cells.[11,12] One randomized, double-blind, multidose pilot study examined I'm-Yunity, a proprietary fractionation of *C versicolor* mushroom extract (Integrated Chinese Medicine Holdings, Ltd., Hong Kong, China), in 15 splenectomized dogs with a histopathologic diagnosis of splenic hemangiosarcoma. Median time to development or progression of abdominal metastases was significantly delayed in dogs receiving 100 mg/kg/d I'm-Yunity (112 days; range 30–308 days) compared with dogs receiving 25 mg/kg/d (30 days; range 16–126 days; $P = .046$), but was not significantly different than in dogs receiving 50 mg/kg/d; however, there was no placebo group. No adverse events were reported.[8]

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

Skorupski and colleagues[14] examined the protective effects of a combination of S-adenosylmethionine (SAMe) and silybin (Denamarin; Nutramax Laboratories, Edgewood, MD) for lomustine (CCNU)-induced hepatotoxicity in 50 dogs. SAMe is found naturally in the body, and silybin is a flavonolignan of milk thistle (*Silybum marianum*).[15] In this study, cancer-bearing dogs with normal alanine aminotransferase (ALT) activities were randomized to receive CCNU (± corticosteroids) alone or with concurrent Denamarin, and plasma biochemical analysis was performed before each dose. More dogs receiving CCNU alone had an increase in ALT compared with dogs receiving CCNU with Denamarin (84% vs 68%). Denamarin is often recommended for dogs prescribed CCNU, because hepatocellular damage is likely decreased and the chance of completing a course of chemotherapy is increased.[14]

Canine high-grade B-cell lymphoma is often used as a model for human non-Hodgkin lymphoma. Because epidemiologic studies indicate that soy-containing diets are associated with a lower incidence of many human tumors, an in vitro study using 2 canine B-cell lymphoid cell lines evaluated genistein (4,5,7-trihydroxyisoflavone), a readily available isoflavone found in soy-based products, and genistein-combined polysaccharide (GCP). Both genistein and GCP led to cell death via apoptosis, and the treated cells exhibited increased Bax:Bcl-2 ratios.[16] GCP was also found to inhibit cell proliferation, increase apoptosis, and induce G_2/M arrest in 3 human and 4 canine lymphoid cell lines.[17] However, an in vivo, dose-escalating pharmacokinetic study determined that therapeutic serum levels of genistein were not reached with oral dosing of GCP in normal dogs.[16]

In an in vitro study in canine osteosarcoma D-17 cells, treatment with α-mangostin, a xanthone derived from the mangosteen fruit (*Garcinia mangostana*), resulted in nuclear condensation and fragmentation, typical of apoptosis.[18] Other reported antitumor effects are in human breast and prostate cancer and leukemia.[19]

HERBS/BOTANICS EVALUATED IN VIVO OR IN VITRO IN OTHER SPECIES

A few in vivo and in vitro studies in other species demonstrate effects of herbs and their antitumor mechanisms. However, most of these treatments seldom progress to quality multi-institutional RCCTs that evaluate response rate and survival. **Table 1** lists some herbs that have been evaluated for their anticancer effects and seem targeted for more research.

Some studies, including human pharmacokinetic studies, have been performed with extracts of herbs, including curcumin, ginseng, ginkgo, ginger, and milk thistle.[20] Curcumin has been reported to influence many cell signaling pathways involved in tumor initiation and proliferation. Its use has been limited because of low bioavailability, which has been overcome with recent innovations in encapsulation and nanoparticles; the herb can now be found in combination formulas such as ProstaCaid and BreastDefend (ecoNugenics, Santa Rosa, CA).[21,22]

Hydrophobic flavonoids from *Scutellaria baicalensis* and the polyphenol honokiol from *Magnolia officinalis* have undergone in vivo and in vitro studies. The former has been evaluated in skin cancer, pancreatic cancer, lymphoma, myeloma, lung cancer, and carcinoma, with reported antitumor mechanisms such as oxidative radical scavenging, attenuation of NF-κβ activity, inhibition of gene regulation of the cell cycle, and

Table 1
Herbs that have been evaluated in vivo and/or in vitro in species other than dogs

Herb	Active Ingredients	Modes of Action
Angelica (Korean *Angelica gigas* Nakai)	Decursin, decursinol	Decreased angiogenesis, inhibition of VEGF
Artemisinin (*Artemisia annua,* Chinese wormwood)	Artemisone, artesunate, dihydroartemisinin	Apoptosis, decreased NF-κB, inhibition VEGF, chemosensitization, reduced MMPs
Astragalus (*Astragalus membranaceus*)	Bioactive polysaccharide, flavonoids, calycosin	Cell-mediated immune mechanisms stimulated, MDR reversal, inhibition of VEGF and HIF-1α
Atractylodes	Bioactive polysaccharides, lactone	Inhibition of proteolysis inhibiting factor, reduction of cytokines
Boswellia (frankincense)	Boswellic acid (ABKA and KBA)	Anti-inflammatory, inhibition of MMP and leukotrienes
Bupleurum (*Radix Bupleuri*)	Saikosaponins	Increased Fas/Fas ligand apoptotic system, inhibition of COX-2 and reactive oxygen species (ROS)-mediated apoptosis
Carthamus	Safflower polysaccharide	Apoptosis, increased cytotoxic NK cells
Coptis	Berberine	Bax/Bcl-2 apoptosis, activation of caspase and PARP
Curcumin (*Curcuma longa*)		Inhibition of COX-2, cyclin D1, and MMPs; inhibition of NF-κB, STAT, and TNF-α signaling; p53 expression regulation; inhibition of I3K/akt signaling
Gingko biloba	Flavonoid glycosides	Increased free-radical scavengers systems (SOD, catalase, glutathione)
Ginseng (*Panax ginseng*)	Ginsenosides	Immunomodulation, activated p53, inhibition of NF-κB, ROS generation
Ginger (*Zingiber officinale*)	6-shogaol, acetoxychavicol acetate, terpenes	Decreases chemotherapy-induced nausea and vomiting, apoptosis via p53 and caspase 3, down-regulation of anti-apoptotic proteins, inhibition of NF-κB and TNF-α, increased antioxidant enzymes SOD, catalase, and GPx

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Table 1
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Herb	Active Ingredients	Modes of Action
Licorice (*Glycyrrhiza glabra*)	Isoliquiritigenin (phenol)	Inhibition of VEGF and MMP 2,9
Magnolia (*M officinalis*)	Magnolol, lignin, honokiol polyphenol	Apoptosis via cleavage of caspase 8 and PARP; inhibition of HIF-1α, VEGF, AMPK, MMP 2,9, and histone deacetylases; decreased COX2, PGEα, and TNF-α
Milk thistle (*S marianum*)	Silybin (flavonoid), silibinin (flavonolignan)	Enhanced expression of TNF-related apoptosis-inducing ligand death receptors; inhibition of NF-κB & VEGF
Mistletoe (*Viscum album*)	Mistletoe lectin	Acts as pattern-recognizing ligands activates T-cell response against cancer cells
Panax notoginseng	Ginsenosides (protopanaxadiol and panaxydol)	Hemostasis, apoptosis, G_1 phase arrest, caspase 3 activation
Rehmannia	Acteoside (phenylpropanoid glycoside)	Down-regulation of tyrosinase activity, activation of p53 apoptosis, decreased TNF-α and IL1-β
Skullcap (*S baicalensis*, Chinese skullcap)	Baicalin, wogonin hydrophilic flavonoids	Apoptosis via PI3K/akt signaling, inhibition of IL-6, decreased MMP-2

Abbreviations: ABKA, 3-O-acetyl-11-keto-beta-boswellic acid; Akt, cytosolic protein kinase; AMPK, adenosine monophosphate-activated protein kinase; Bax/Bcl-2, Bcl-2 associated X protein/B-cell lymphoma-2; COX-2, cyclooxygenase-2; GPx, glutathione peroxidase; HIF-1α, Hypoxia inducible factor 1 alpha; IL1-β, interleukin (IL)-1b beta; IL-6, interleukin-6; KBA, 11-Keto-β-boswellic acid; MDR, multidrug resistance; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light chain enhancer of activated B-cells; PARP, poly-ADP ribose polymerase; PGEα, prostaglandin E2 alpha; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.
Data from Refs.[15,23,25–27,32,102–162]

suppression of cyclooxygenase-2 (COX-2) gene expression with almost no effects on normal cells.[23–25] Bladder, lung, skin, and breast cancer research (in vivo and in vitro) has evaluated mechanisms of honokiol.[26]

Milk thistle, with the active ingredient silibinin, a flavonolignan, has been studied in colon, prostate, and lung cancers. It is also being developed into topical and injectable formulations,[27] demonstrating that preparations may be standardized, safety margins known, and research and marketing can be successful.

BIOACTIVE POLYSACCHARIDES: FUNGI

β-D-Glucans, now termed bioactive polysaccharides, are high-molecular-weight, complex branch-chained polysaccharides found especially in fungi with specific

configurations of β1-3, 1-4, or 1-6 branch chains, which have been shown to have immunostimulating activities. The importance of their structure-function relationship has been reported in studies looking at their immunomodulating activity, including activation of macrophages, monocytes, natural killer (NK) cells, dendritic cells (DCs), and lymphocytes. These bioactive polysaccharides have been shown to have antitumor effects in lung, breast, cervical, and prostate cancer, and melanoma.[28]

Immunomodulating activity has been shown to be due to glucan receptors on cell surfaces, such as monocytes and other immune cells. Fungal polysaccharides, such as *Agaricus blazei, Cordyceps sinensis, Ganoderma* species, and *G frondosa*, have been systematically studied for development into nutraceuticals and include established drugs polysaccharide-K (PSK, Krestin; Kureha Chemicals Industry Corp., Tokyo, Japan) from *Trametes versicolor* (Tv mushrooms), and lentinan from *Lentinus edodes*. Variable bioactivity may be due to differences in receptor affinity or receptor-ligand interaction. The immunomodulation action is via differing receptors involving dectin-1, toll-like receptors (TLR), and an increase of antioxidant capacity.[28]

A phase I/II dose escalation study using orally administered preparations from Tv in 9 women with breast cancer after standard chemotherapy and radiotherapy concluded that up to 9 g/d was safe and tolerable in the immediate posttreatment setting and may improve immune status in immunocompromised patients with breast cancer.[29] A larger phase I/II dose escalation trial of 32 postmenopausal patients with breast cancer free of disease after initial treatment was performed using a maitake liquid extract. The primary endpoints were safety and tolerability, but the study demonstrated a statistically significant association between maitake and immunologically stimulatory and inhibitory measurable effects in peripheral blood.[30]

A meta-analysis of 5 RCCT studies evaluated clinical and adverse effects of *Ganoderma lucidum* in patients with cancer. The following parameters were described: tumor response, evaluated according to the World Health Organization criteria; immune function parameters, such as NK cell activity; and QOL, measured by the Karnofsky scale. Patients who had been given *G lucidum* with chemo/radiotherapy were more likely to respond, whereas *G lucidum* treatment alone did not demonstrate the same regression rate as that seen in combined therapy, supporting its use as an adjunct to conventional treatment. The results suggested that *G lucidum* potentially stimulates host immunity and tumor response, but concluded uncertainty in enhancement of long-term survival.[31]

These bioactive polysaccharides possess other antitumor properties whose exact mechanisms are unknown, such as stimulation of cell differentiation, hematopoiesis, antimetastasis, and anti-angiogenesis.[32,33] A direct and/or synergistic response in tumor regression has been shown in animal studies with mammary carcinoma, metastatic lung metastasis, gastric carcinoma, and melanoma.[34,35] It is possible that specific glucans have a role in triggering complement-dependent antitumor cytotoxicity. A synergistic effect with tumor regression was evident with administration of β-D-glucans together with monoclonal antibodies against GD2 ganglioside, G250 protein, and CD20 protein in experimental neuroblastoma, carcinoma, and CD20+ lymphoma, respectively.[36]

The turkey tail mushroom (*C versicolor, T versicolor*) is one of the most studied mushrooms, with extracts such as PSK, PSP, Tv polysaccharides, and versicolor polysaccharide affecting different cancer cell lines.[37] Peer-reviewed publications on their antitumor effects include 37 in vitro articles, 55 animal studies, 43 human clinical studies, and 11 review articles in gastrointestinal, breast, and lung cancer. In vitro data suggest that the immunologic effects of PSK are mediated through TLR (transverse cell membrane proteins located on DCs and macrophages) and stimulation of TNF secretion; they are TLR-4-dependent, but dectin-1 independent. These innate

immune cells respond to foreign invaders and at the same time trigger the release of inflammatory cytokines that activate T and B cells. TLRs link innate and active immunity in a specific recognized role.

A meta-analysis of PSK trials in colorectal cancer showed a positive impact on clinical outcomes. Tv is standard for oncology treatment in mainstream, modern Japanese cancer management, and PSK was approved in 1977 as a cancer therapy by the Japanese National Health Registry. It now represents 25% of the total national costs of cancer care in Japan.[37]

Three randomized trials (n = 227, 376, 914 women) evaluated PSK immunotherapy (3000 mg/d) in patients with breast cancer. PSK treatment resulted in significantly extended survival times when added to standard protocols, or comparable survivals to conventional chemotherapy.[37] At the time of this writing, the National Institutes of Health/National Center for CAM was considering funding for a breast cancer clinical trial using PSK, with collaboration between Fred Hutchinson/University of Washington Cancer Consortium and Bastyr University.

ACUPUNCTURE

Acupuncture involves the stimulation of A delta nerve fibers, which then activate interneurons in the dorsal horn of the spinal cord; produce encephalins and other endogenous opioids, anti-inflammatory cytokines, and neuropeptides; and may also inhibit C nerve fibers in the dorsal horn. An abundance of animal studies is published suggesting acupuncture for analgesic use, but the clinical evidence from RCCTs in noncancer patients has not been able to demonstrate that acupuncture is conclusively superior to sham acupuncture for analgesia.[2,38] Currently, there are no studies on acupuncture in dogs or cats with cancer, but human studies suggest benefits in pain management, anorexia, gastrointestinal effects, and QOL.

Research in human acupuncture demonstrates potential uses for specific cancer-related complications. In a breast cancer study evaluating upper limb lymphedema, postsurgical arm circumference improved in acupuncture-treated patients.[39,40] Similarly, in another study using acupressure in human patients with colorectal cancer, there was shortened time to first flatus passage and oral liquid intake, and improved gastrointestinal function in patients after abdominal surgery.[41]

Overall, the literature supports the use of acupuncture for cancer-related pain management, but concern is repeatedly expressed about methodology and sampling bias.[42,43] One review suggested protocols generated from RCCTs should be adopted by clinicians using acupuncture and that clinicians should possess knowledge and skills in both acupuncture and allopathic oncology.[38]

Several studies support the use of acupuncture to treat chemotherapy-induced nausea/vomiting, but a need for more research and repeatable protocols is emphasized. These studies evaluated acupressure, electro-acupuncture, as well as traditional acupuncture.[1,44] Defining specific endpoints and study designs are issues with studies evaluating acupuncture for cancer-related fatigue and QOL.[45]

DIETARY SUPPLEMENTS EVALUATED IN DOGS OR IN VITRO CANINE CELLS AND RELEVANT STUDIES IN OTHER SPECIES OR IN VITRO

A 2004 review of nutrition and supplements as complementary therapy in pets with cancer included the following key nutritional factors: soluble carbohydrate, fiber, protein, arginine, fat, and omega-3 (N-3) fatty acids (FAs). It also includes a brief discussion of nutraceuticals, including antioxidant vitamins, trace minerals, glutamines, protease inhibitors, garlic, tea polyphenol, vitamin A, and shark cartilage.[5] More

current studies looking at these and other nutrients and their role in cancer in the dog and canine cell lines are evaluated in later discussion.

Calcitriol

Calcitriol (1,25-dihydroxycholecalciferol; 1α25-dihydroxycholecalciferol), the principal biologically active form of vitamin D, exerts potent antineoplastic activity in vitro and in vivo in a broad range of tumor model systems. Calcitriol induces G_1/G_0 cell-cycle arrest and apoptosis, while down-regulating Bcl-2, decreasing epidermal growth factor, and inhibiting tumor invasion through decreased metalloproteinase (MMP)-2 and metalloproteinase-9 activity.[46,47] Calcitriol was synergistic with cisplatin using in vitro canine tumor cells and a phase I clinical study to determine the maximum tolerated dose (MTD) of this combination in dogs with cancer and to characterize the pharmacokinetics of calcitriol in dogs.[47] An open-label, single-dose, 2-way crossover study with dogs randomly receiving calcitriol either intravenously or orally, followed by cisplatin, demonstrated a lower MTD of cisplatin when receiving calcitriol in 10 tumor-bearing dogs studied. Conclusions were that high-dose oral calcitriol has moderate bioavailability and individual variability is similar to that reported in humans. Serum levels in some dogs were at the level shown to have antitumor activity in a preclinical murine model.[48]

Calcitriol exhibits synergistic, antiproliferative in vitro activity when used with other chemotherapeutics, including CCNU, vinblastine, imatininib, or toceranib. A study using canine mastocytoma C2 cells reported calcitriol increases chemotherapy or tyrosine kinase inhibitor cytotoxicity. The study also used a highly concentrated formulation of calcitriol as a single therapy in dogs with mast cell tumors. Remission was obtained in 4 of 10 dogs, but the study was discontinued because of adverse events.[49]

Calcitriol inhibited canine transitional cell carcinoma cells via G_0/G_1 cell-cycle arrest.[50] Calcitriol has also been shown to inhibit proliferation and induce apoptosis in 2 types of human bladder cancer cells and *N*-methyl nitrosourea–induced rat tumors.[51] Recent studies demonstrate that the antiproliferative effects of calcitriol are mediated by the nuclear vitamin D receptor (VDR), with one study reporting improved survival associated with an increase in VDR expression in lung adenocarcinoma cells.[52]

Retinoids

Retinoids are needed for normal cell signaling, and studies have evaluated this vitamin for cancer protection and treatment. Retinoids are used to treat cancers via their actions on cell differentiation, proliferation, and apoptosis. In humans, retinoids are used in treatment of acute promyelytic leukemia (APL), medulloblastoma, and metastatic melanoma. They enhance effects of chemotherapeutics such as cisplatin in ovarian carcinoma, squamous head and neck cancers, hepatoma, and lung and breast cancers. The primary limitation of the use of retinoids is retinoid resistance, which is well identified in APL.[53]

A 42% response rate to retinoid treatment has been seen in dogs with cutaneous lymphoma, and positive results have been seen with in vitro canine mast cells and osteosarcoma cell lines.[54] Numerous clinical studies are using new and synthetic retinoids, alone or in combination therapy, for the treatment of breast, ovarian, renal, head and neck, melanoma, and prostate cancers in human oncology; overall, results continue to be promising.[53,55,56]

Antioxidants

Use of antioxidants in oncology patients has been controversial. It has been hypothesized that selenium supplementation exerts an anticarcinogenic effect by reducing

the naturally occurring genotoxic stress within the aging prostate. In a translational RCCT using 49 intact male elderly beagles, the extent of DNA damage in prostate cells and in peripheral blood lymphocytes was lower among the selenium-supplemented dogs.[57] In another randomized study, data from elderly beagles being supplemented with selenium as a model for prostate cancer were compared with data from 2 humans. Six markers of prostatic homeostasis that likely contribute to prostate cancer risk reduction were measured in the aged beagles—intraprostatic dihydrotestosterone (DHT), testosterone (T), DHT:T, epithelial cell DNA damage, proliferation, and apoptosis.[58]

The human literature suggests a decrease in peripheral neuropathy associated with paclitaxel with vitamin E, glutamine, and L-carnitine supplementation. Vitamin E with glutamine decreased severity of oral mucositis resulting from radiation and chemotherapy, and glutamine and probiotics can reduce chemotherapy-induced diarrhea.[59] Vitamin E delta-tocotrienol significantly enhanced the efficacy of gemcitabine to inhibit pancreatic cancer growth and survival in vitro and in vivo.[60]

A review of antioxidant use in 19 studies using Cochrane Collaboration methodology[61] found no evidence of significant decreases in chemotherapy efficacy. Another review of antioxidants that evaluated glutathione, melatonin, vitamin A, and an antioxidant mixture of *N*-acetylcysteine, vitamin E, selenium, L-carnitine, and Co-Q10 reported either decreased chemotherapy toxicity or no difference with the supplementation of all antioxidants examined except one study of vitamin A, which resulted in increased toxicity.[62] A systematic review of antioxidant use in gastrointestinal cancers appeared to show an increase in overall mortality.[63] Vitamins A, C, E, and selenium, alone or in different combinations, did not prevent lung cancer nor decrease lung cancer mortality, but some evidence showed a small increase in lung cancer mortality in smokers or persons exposed to asbestos and beta-carotene supplements.[64]

Well-designed clinical trials and observational studies are needed to determine the short-term and long-term effects of antioxidants and cancer.[65] At this time, there are no studies nor widely accepted conclusions or extrapolations regarding benefits or problems associated with integrative use of antioxidants in veterinary clinical oncology.

Omega-3 Fatty Acids

Bauer[66] presented a dose strategy for omega-3 (N-3) FAs or N-3 polyunsaturated fatty acid, most notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for various canine diseases. Activities of matrix MMPs are significantly higher in canine malignant mammary gland tumors when compared with normal tissue. N-3 FAs affect activities of MMPs and tissue inhibitors of MMPs in dogs, suggesting potential for dietary modulation of tumor metabolism in dogs.

One clinical trial evaluated the effects of N-3 FA in 32 dogs with lymphoma: treatment dogs received a diet supplemented with menhaden fish oil and arginine, whereas control dogs received an identical diet supplemented with soybean oil. Increasing serum DHA concentration was associated with longer disease-free intervals and survival times in dogs with stage III lymphoma treated with doxorubicin.[66,67] In another study, supplementation with N-3 FA did not affect doxorubicin pharmacokinetics in 23 dogs with lymphoma.[68]

In a randomized, double-blind, placebo-controlled clinical study, 12 dogs with nasal malignant carcinomas were given dietary menhaden oil (DHA and EPA) or soybean oil (control) before radiation therapy (RT). Blood levels of DHA, EPA, insulin, glucose, lactic acid, and MMPs 2 and 9; resting energy expenditure; and inflammatory eicosanoids from nasal biopsies were measured throughout RT. The dogs fed menhaden

oil had significantly higher plasma concentrations of DHA (increased by 500%) and EPA (200%), lower tissue inflammatory eicosanoids, and decreased resting energy expenditure (by 20%) compared with controls. Increased plasma DHA was significantly associated ($P<.05$) with decreased plasma lactic acid and MMPs. This study suggests EPA and DHA may reduce some detrimental inflammatory eicosanoids and metabolic consequences of RT.[69]

Probiotics

Current evidence demonstrates probiotic's role in modulating gut microbiota, improving gut physicochemical conditions, and reducing oxidative stress. Probiotics also inhibit tumor progression, produce anticancer compounds, and modulate the host immune response.[70,71] Evidence strongly suggests NK cells are the antitumor effector cells involved, and NK cell activity correlates with the observed antitumor effect of probiotics in mice. Dendritic cells (DC) are responsible for the recruitment and mobilization of NK cells; therefore, it may be inferred that DCs are most likely to be the acting interphase point.[72]

A large meta-analysis of probiotic use in human gastrointestinal cancer and RT to the abdominal region for cervical, ovarian, prostate, sigmoid, or colorectal cancer showed a beneficial effect.[73,74] Probiotics can improve the gut mucosal barrier by altering fecal microbes and decrease complications in humans undergoing surgery for colorectal cancer[75,76] by reducing the rate of postoperative septicemia through maintenance of gut barrier integrity in patients with colorectal cancer.[77]

RCCTs have demonstrated efficacy of probiotics, such as VSL#3, *Lactobacillus casei* DN-114 001, and other formulations, in decreasing the incidence and grade of RT-induced diarrhea, which is normally found in more than 80% of patients.[73,74,78,79]

A growing body of evidence indicates that changes in gut permeability and translocation of components of the intestinal microflora play a key role in eliciting immune-mediated mechanisms that lead to chronic inflammation, autoimmunity, and neoplasia. Research using an animal model of colorectal cancer and cachexia has shown that an increase in tumor burden leading to cachexia is accompanied by increased gut barrier permeability, elevated plasma endotoxin levels, and evidence of chronic inflammation. Improvements are reported in intestinal function, in addition to weight gain and decreased inflammation, with the use of EPA, immunoglobulin isolates, and probiotics.[80]

Contraindications to probiotic use include potential harm in several populations, including patients with neutropenia or other causes of immunosuppression, intensive care unit patients, patients with central venous catheters receiving parenteral nutrition, and patients requiring administration of the probiotic via a feeding tube.[73] A review of probiotic use in critically ill human patients lists the most commonly reported adverse events: bacteremia, fungemia, and sepsis.[81] A 2-part retrospective study conducted in 2007 to 2008 characterized probiotic use, including the type of prescribing provider, choice of probiotic prescribed, indications for use, presence of potential risk factors for probiotic infection, as well as incidence of probiotic-related bloodstream infections over 8 years. The study concluded probiotic use was associated with a minimal risk of probiotic-related infection (0.2%), despite its use at a high frequency among inpatients at high theoretic risk.[82]

In an RCCT of 40 clinically ill patients randomized to receive placebo or probiotic (VSL#3) for 7 days, patients receiving the probiotic had a reduction in inflammation and improvement of clinical outcome.[80] One systematic meta-analysis of 19 trials that studied more than 2800 infants determined that enteric probiotic supplementation significantly reduced the incidence of severe necrotizing enterocolitis; it is now being considered a standard of care in pediatric medicine. There was no evidence of

significant reduction of nosocomial sepsis, and no systemic infection with supplemented probiotics in this pediatric population. This recent data and a report by the European Society for Pediatric Gastroenterology concluded probiotics could be generally considered safe at least in children.[83]

No studies have been performed in veterinary oncology patients, but the same probiotic mechanisms have been suggested in the dog and cat; therefore, veterinarians should discuss these issues with clients to design personal strategies using available products, sound clinical judgment, and the best current peer-reviewed evidence.

Phytic Acid, Phytate, Myo-Inositol Hexaphosphate

Inositol hexaphosphate (IP6; phytic acid, phytate, myo-inositol hexaphosphate) is a saturated cyclic acid found naturally in bran and seeds of plants and is the principal storage form of phosphorus. Myo-inositol is the structural basis for several secondary messengers, whereas inositol serves as an important component of the structural lipids phosphatidylinositol (PI), its various phosphates, and the phosphatidylinositol phosphate.

No RCCTs of IP6 and canine and feline cancer have been published. Early in vitro research shows IP6 slows abnormal cell division and may sometimes transform tumor cells into normal cells possessing moderate anticancer activity. The most consistent and best anticancer results were obtained from a combination of IP6 and inositol. In addition to reducing cell proliferation, IP6 increases differentiation of malignant cells, often resulting in a reversion to normal phenotype. Exogenously administered IP6 is rapidly taken into the cells and dephosphorylated to lower phosphate inositol phosphates, which further interfere with signal transduction pathways and cell-cycle arrest.[84,85]

A small randomized, pilot clinical study was conducted to evaluate IP6 + inositol in patients with breast cancer treated with adjuvant therapy. Patients receiving chemotherapy, along with IP6 + inositol, did not have cytopenia (platelets and leukocytes), had a significantly better QOL ($P = .05$) and functional status ($P = .0003$), and were able to perform their daily activities.[86]

Current literature supports the use of IP6 and is revealing the antitumor mechanisms of IP6 in vivo and in vitro, especially for breast, colorectal, and prostate cancer. Myo-inositol trispyrophosphate (ITPP), a molecule that increases oxygenation of tumor cells, increases survival of mice in a model of carcinomatosis.[87] In vitro work demonstrates that ITPP treatment increases oxygen tension and blood flow in melanoma and breast cancer models.[88]

Another study evaluated the effect of IP6 extracted from rice bran on azoxymethane-induced colorectal cancer in rats. IP6 was given via drinking water for 16 weeks, which markedly suppressed the incidence of tumors compared with the control.[89] The in vivo chemopreventive efficacy of IP6 in a mouse prostate model has also been studied using anatomic and dynamic contrast-enhanced magnetic resonance imaging.[90] A metabolomics study using quantitative high-resolution H-NMR on prostate tissue extracts showed that IP6 significantly decreased glucose metabolism and membrane phospholipid synthesis, in addition to causing an increase in myo-inositol levels in the prostate. These findings show that oral IP6 supplementation blocks growth and angiogenesis in a prostate cancer model in conjunction with metabolic events involved in tumor sustenance. The results demonstrate that energy deprivation within the tumor suppresses growth and progression of prostate cancer.[90]

An in vitro study of 3 human cancer cell lines not only confirms that IP6 alone inhibits the growth of breast cancer cells but also that IP6 acts synergistically with adriamycin or tamoxifen.[91] IP6 (2 mM) strongly inhibited both growth and proliferation, decreased

cell viability, and caused a strong apoptotic death of human prostate cancer cell line, PC-3; similar effects were observed in other human cancer cell lines. These findings established, for the first time, IP6 efficacy in inhibiting aberrant epidermal growth factor receptor (EGFR) or insulin-like growth factor-1 receptor pathways; this inhibition appears to promote survival signaling cascades in advanced and androgen-independent human prostatic cancer cell lines. In another study using PC-3 tumor xenograft growth in nude mice, 2% (w/v) IP6 given in drinking water inhibited tumor growth and weight by 52% to 59% ($P<.001$). Immunohistochemical analysis of xenografts showed that IP6 significantly reduced expression of molecules associated with cell survival/proliferation (ILK1, phosphorylated Akt, cyclin D1, and proliferating cell nuclear antigen) and angiogenesis (platelet endothelial cell adhesion molecule-1 or CD31, vascular endothelial growth factor, endothelial nitric oxide synthase, and hypoxia-inducible factor-1α) together with an increase in apoptotic markers (cleaved caspase-3 and poly [ADP-ribose] polymerase [PARP]). These findings suggest that, by targeting the PI3K-ILK1-Akt pathway, IP6 suppresses cell survival, proliferation, and angiogenesis and induces prostate cancer cell death, which might have translational potential in preventing and controlling the growth of advanced and aggressive prostate cancer.[92,93]

In human colon cancer cells, IP6 up-regulates basal mRNA expression of some MMPs and their tissue inhibitors and down-regulates MMP-1, MMP-2, MMP-3, and MMP-9. IP6 could be an effective antimetastatic agent.[94]

Transforming growth factor-β (TGF-β) is a multifunctional cytokine involved in the regulation of cell development, differentiation, survival, and apoptosis with activity in neoplastic cells. In a study using colon cancer cells, another anticancer role of IP6 was shown to be enhancing the expression of the TGF-β gene and its receptors at the transcriptional level.[95]

USING IM IN VETERINARY CLINICAL ONCOLOGY

There is little high-level evidence to support use of HDS and acupuncture in veterinary clinical oncology; however, it seems reasonable to make some extrapolations, especially when considering the large amount of information from in vivo and in vitro studies in other species and the prospect of translational research. Brown and Reetz[8] set a standard with their small pilot study of PSP extract from *C versicolor*. A larger RCCT comparing effectiveness of the extract to that of doxorubicin in dogs with splenic hemangiosarcoma has been initiated.[96]

Collaboration between conventional oncologists and practitioners of IM, who have knowledge, experience, and training to use HDS and acupuncture, is needed to explore the possibilities of integrative veterinary oncology using logical, science-based practices (Erin Bannink, DVM, DACVIM [oncology], Bloomfield Hills, MI, personal communication, 2013; and Steve Marsden, DVM, ND, MSOM, L.Ac, Dipl. CH, RH [AGH], Edmonton, Alberta, Canada, personal communication, 2013). Although individual herbs are discussed here, integrative practitioners more often use herbal formulas and have identified safe, reliable sources of HDS products with known content; they also know possible interactions and understand dosing to prevent adverse effects.[10,97] Veterinarians with this special training, education, and experience can be found through the organizations in **Box 1**.

ADVERSE REACTIONS: DRUG-HERB INTERACTIONS

The most common drug-herb interactions likely occur due to altered expression of the functional CYP450 isoenzymes that metabolize chemotherapeutic drugs. A change in

Box 1
Sources of information about using IM in patients with cancer

- College of Integrative Therapy: www.civtedu.org
- Veterinary Information Network (message boards): www.vin.com
- American College of Veterinary Nutrition: www.acvn.org
- American Holistic Veterinary Medicine Association: www.ahvma.org
- Veterinary Botanical Medical association: www.vbma.org
- American Academe of Veterinary Acupuncture: www.aava.org
- International Veterinary Acupuncture Society: www.ivas.org

P glycoprotein (P-gp), which mediates transmembrane drug transport, is also a potential source of adverse interactions. The most notable herb-drug interaction is with *Hypericum perforatum*, more commonly known as St. John's Wort (SJW), which interferes with both CYP450 isoenzymes and P-gp. Clinical implications of drug-herb interactions depend on a variety of factors, such as dose, timing of herbal intake, dosage, route of drug administration, therapeutic range, and individual variation, including differences in the patient's diet, age, health status, genetics, and metabolizing capacity.[98,99]

A total of 66 clinical pharmacokinetic interaction studies were identified for the most frequently used herbal drugs in the United States, Canada, and Europe; the clinical evidence was most robust and informative for gingko biloba (21 studies) and milk thistle/silymarin (13), and appears limited for ginseng (9), goldenseal/berberine (8), garlic (8), and echinacea (7 studies). At commonly recommended doses, none of these herbs acted as potent or moderate inhibitors or inducers of cytochrome P450 (CYP) enzymes or P-gp.[100]

The occurrence of clinical CYP3A4-mediated interactions between anticancer drugs and SJW, milk thistle, and garlic correlated with results obtained with midazolam as a predictor of pharmacokinetic interactions. Caution is warranted when combining SJW with other anticancer drugs metabolized by CYP3A4; garlic and milk thistle were presumed safe, and no recommendation could be made for ginseng. In vitro data using CYP3A4 can likely be extrapolated to clinical studies, but clinical pharmacokinetic interactions are complicated by several factors (eg, poor pharmaceutical availability, solubility, and bioavailability of HDS). Veterinary chemotherapy drugs that use the CYP3A4 enzyme include vincristine, vinblastine, and EGFR-TK inhibitors.[101]

Curcumin, quercetin, proteolytic enzymes, ginkgo, and selenium are recommended to be discontinued during RT. Certain HDS may interfere with coagulation and are a consideration in cancer surgeries, including IP6, vitamins A and E, curcumin, and ginseng. A more comprehensive list[99] of potential interactions has been compiled, and consultation with veterinarians specializing in HDS, oncology, and nutrition to obtain the most current information is recommended.

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