Nutraceuticals for Canine Liver Disease: Assessing the Evidence

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INTRODUCTION

Therapeutic agents, called hepatoprotectants, have been promoted for their potential role in the ancillary treatment of liver disease in dogs and cats. These products include both prescription drugs and nondrug dietary supplements. A drug, by definition, refers to “any substance, food, or nonfood that is used to treat, cure, mitigate, or prevent a disease and any nonfood substance that is intended to affect the structure or function of man or animals.” To become a drug, a compound

KEYWORDS

• Nutraceuticals • Dietary supplement • Liver • Evidence

KEY POINTS

• Until greater regulatory oversight of nutritional supplements is required, veterinarians will need to weigh the costs, risks, and potential benefits of nutritional supplements for their patients on an individual basis.
• Veterinarians should strive to maintain a critical view of nonscientific promotional material and rely primarily on scientific evidence.
• Before recommending or administering a nutritional supplement to canine patients with the intent of providing hepatoprotection, veterinarians should obtain informed consent from the owners to ensure they understand that little to no evidence exists to support the use of these products for the treatment or prevention of liver disease.
• Veterinarians also must be aware that lack of adequate regulation of so-called nutraceuticals increases the risk of lack of quality control, labeling inaccuracies, and omission of cautionary statements.
• Although some dietary supplements have shown beneficial effects under limited in vitro conditions or for a very specific hepatotoxin, their general use as global hepatoprotectants remains questionable.

INTRODUCTION

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A drug, by definition, refers to “any substance, food, or nonfood that is used to treat, cure, mitigate, or prevent a disease and any nonfood substance that is intended to affect the structure or function of man or animals.” To become a drug, a compound
must undergo an extensive drug approval by competent authorities such as the US Food and Drug Administration (FDA) and European Medicines Agency, and be shown to be safe and effective for its intended use.

Under the Dietary Supplement Health and Education Act of 1994, the term dietary supplement is defined as a product taken by mouth that contains a dietary ingredient intended to supplement the diet. The dietary ingredients in these products can include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, and metabolites. Dietary supplements can also be extracts or concentrates, and can be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. These different definitions apply to human consumers and not pets.

The term nutraceutical was coined from “nutrition” and “pharmaceutical” in 1989 and was defined as, “a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease.” According to the North American Veterinary Nutraceutical Council, a nutraceutical is “a substance produced in purified or extracted form which, when administered orally to patients, aims to provide them the necessary elements for their structure and normal function to better their health and well-being.” However, the term nutraceutical as commonly used in marketing has no regulatory definition, because only a registered drug may have indications against diseases. Because the term nutraceutical has no regulatory or legal definition, the authors will refer to these compounds as nutritional or dietary supplements.

For a limited number of compounds, veterinarians may find formulations that are classified as drugs if the compound is formulated one way (ie, injectable) for a specific indication, and the same or similar compounds have been classified as a nutritional supplement if formulated a different way (ie, oral) without a specific indication. The veterinarian should be assured that if the product is an FDA-approved drug, it has undergone safety and efficacy testing for the specific indication on the label. The same is not true for the nutritional supplement. One example is chondroitin sulfate, a compound frequently touted for treating canine osteoarthritis. An injectable form of polysulfated glycosaminoglycans, containing primarily chondroitin sulfate, is FDA-approved for intramuscular injection to control signs associated with noninfectious degenerative and/or traumatic arthritis of canine synovial joints. Numerous nutritional supplements containing chondroitin sulfate for oral administration are marketed, but none have undergone the rigid safety and efficacy studies required for FDA approval. Because oral bioavailability of many nutritional supplements is limited, evidence of a compound’s efficacy via parenteral administration should not be used to justify its use via oral administration.

The veterinary profession has ethical obligations to ensure effective and safe treatment and to base therapeutic decisions on scientific evidence. It important to know the true efficacy and safety of products, such as dietary supplements, that are used in veterinary medicine. Because these products are often promoted as “natural,” pet owners may have the misconception that they are safer than drugs. These products may be used widely by pet owners because they can purchase them directly at health food stores or on the Internet. Therefore, veterinarians must have a thorough understanding of the safety and efficacy of dietary supplements in veterinary patients. This article focuses on several dietary supplements suggested to be useful for treating liver diseases in dogs.

HEPATOACTIVE DIETARY SUPPLEMENTS: WHAT CAN BE FOUND IN THE SCIENTIFIC LITERATURE?

With MEDLINE, no “MeSH term” (Medical Subject Headings term) can be identified for “Nutraceuticals.” Instead “Dietary Supplements” is proposed. When the equation
(‘Dietary Supplements’[MeSH] AND ‘Liver Diseases’[MeSH] AND ‘Dogs’[MeSH]) is used in MEDLINE, CAB Abstracts, and Google Scholar, very few research papers are identified. Only 9 research papers are useful for analysis (Table 1). No relevant reference is identified in the databases about efficacy of vitamin E. However, very detailed narrative reviews about hepatoprotectants were published by Center in 2004 (a review of 105 pages) and Webster and Cooper in 2009 in *Veterinary Clinics of North America: Small Animal Practice*, which provide a thorough description of the physiopathology of liver diseases (mechanisms of hepatocyte cell death, oxidative stress) and possible actions of food and nonfood products that are called hepatoprotectants. Dietary supplements that are commonly listed as “hepatoprotectants” include SAMe, yutan (which contains ursodeoxycholic acid [UDCA]), and silymarin (derived from the milk thistle plant).

**SAME**

SAMe has been marketed for use in dogs with liver disorders. It is purported to have antiinflammatory and antioxidant effects, and to play a role in cellular replication and protein synthesis. SAMe is an endogenous molecule produced from the amino acid methionine and plays a central role in the transsulfuration process that generates glutathione. Glutathione, an antioxidant and free radical scavenger, serves as a major physiologic defense mechanism against oxidative stress in hepatocytes. Decreases in hepatic glutathione levels have been described in dogs and cats with severe liver disease. Although specific indications for nutritional supplements are not allowed by the FDA, SAMe is often recommended as an adjunct treatment of necroinflammatory, metabolic, and cholestatic hepatopathies in dogs and cats. At the recommended dose of 20 mg/kg/d orally, a low incidence of side effects has been reported. Nausea or refusal of food, vomiting, and anxiety may occur in the postpill interval (hours).

Data supporting the use of SAMe in canine and feline patients is minimal. In 2002, SAMe was reported to be useful in a case of acetaminophen toxicity. However, because this was a single case report, any potential beneficial effects of SAMe cannot be confirmed. In 2005, Center and colleagues assessed the influence of orally administered SAMe on clinicopathologic and hepatic effects induced by long-term (84 days) administration of prednisolone in dogs. The study compared 2 groups of 4 animals (n = 8). Despite the fact that SAMe-treated dogs were not protected from the classic clinicopathologic and histopathologic features (vacuolar hepatopathy) associated with so-called steroid hepatopathy, the authors concluded that administration of 20 mg/kg/d of SAMe may mitigate the apparent pro-oxidant influences of prednisolone. Despite the lack of data supporting the use of SAMe as a hepatoprotectant, the compound is frequently recommended for dogs with hepatobiliary disease. Before veterinarians recommend use of SAMe, they should ensure that owners understand (informed consent) that data on its efficacy are lacking.

**YUTAN**

Yutan, a Chinese compound derived from the dried bile of the Chinese black bear, has been used for centuries for its purported hepatobiliary healing powers. In 1936, UDCA was identified as the major bile acid responsible for Yutan’s hepatoprotective effects. Currently, synthetic forms of UDCA are available as an FDA-approved human drug that is specifically indicated for the treatment of primary biliary cirrhosis. Its beneficial effects may be from replacement of more toxic bile acids in the bile acid pool, stimulation of choleresis, antiapoptotic effects, stabilization of mitochondrial function, and/or immunomodulatory actions. Despite its limited indication in humans,
## Table 1
Articles assessing the clinical efficacy of potential hepatoprotective nutritional supplements in dogs

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Date</th>
<th>Journal</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term effects of N-acetylcysteine and ischemic preconditioning in a canine model of hepatic ischemia-reperfusion injury</td>
<td>Baumann J, et al¹²</td>
<td>2008</td>
<td>Eur Surg Res</td>
<td>Experimental in vivo trial (induced hepatopathy)</td>
</tr>
</tbody>
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(continued on next page)
it has been recommended (10–15 mg/kg/d orally) for the treatment of cholestatic, necroinflammatory, metabolic, and immune-mediated hepatopathies in dogs.\textsuperscript{15} Three case reports represent the only scientific data supporting the use of UDCA for treating hepatobiliary diseases in the dog.\textsuperscript{6,7}

**SILYMARIN**

Silymarin is derived from the milk thistle plant (\textit{Silybum marianum}) which grows worldwide and has been used in Europe for more than 2000 years as a home remedy for liver disease in man.\textsuperscript{19,20} A standard milk thistle extract contains 60% to 70% silymarin, which is composed of a mixture of flavonolignans, such as silibinin (silybin), isosilibinin (isosilybin), silidianin (silydianin), and silichristin (silychristin), with silibinin being the major active component.\textsuperscript{20} Silymarin is thought to exert antioxidant, anti-inflammatory, and antifibrotic effects.\textsuperscript{15,19} At suggested doses (50–250 mg/kg orally, twice per day),\textsuperscript{21} no adverse effects have been reported. However, silymarin may inhibit the activity of drug-metabolizing enzymes.\textsuperscript{15} However, silibinin has poor oral bioavailability.\textsuperscript{22}

In 1984, Vogel and colleagues\textsuperscript{9} investigated the use of intravenous silibinin for the treatment of amanita mushroom toxicity in beagles. A single oral dose of the lyophilized death cap fungus \textit{Amanita phalloides} was administered to experimental dogs (n = 23). Twelve dogs served as controls, whereas the remaining 11 were treated with 50 mg/kg of silibinin intravenously at 5 and 24 hours after intoxication. The investigators subjectively reported that gastrointestinal signs were of lesser severity in animals treated with silibinin, but no objective data or scoring system was provided. Of the 12 dogs given \textit{A phalloides} but not treated with silibinin, 4 died with signs of hepatic coma and histopathologic evidence of widespread hemorrhagic hepatic necrosis. All 11 silibinin-treated dogs survived. Although several parameters that indicate liver disease were measured (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AP], bilirubin, and prothrombin time) neither means, medians, nor individual animal values were reported. Figures plotting these values over time were provided and the authors reported that abnormal values were less pronounced in silibinin-treated animals than in the controls. However, no statistical comparisons were made. Furthermore, it should be noted that silibinin was administered intravenously and therefore, by definition, cannot be considered a nutraceutical.

In 1990, Paulova and colleagues\textsuperscript{10} tested the efficacy of silymarin for treating tetrachloromethane-induced liver disease in dogs. The information provided is taken from the abstract only because an English language version of the article was not available. Sixteen beagles (n = 16) were divided into 4 groups of 4 animals. Three groups were administered a dose of tetrachloromethane in sunflower oil by mouth. A negative
control group was given sunflower oil only. Silymarin was evaluated separately as a preventive (silymarin administered 4 days before tetrachloromethane; n = 4) and as a treatment (silymarin administered 4 days after tetrachloromethane; n = 4). The authors reported that the ability of silymarin to protect the liver was low.

**COMBINATION OF SAME AND SILYMARIN**

A recent prospective randomized controlled trial assessed a commercially available veterinary product containing a stable salt of SAMe and silybin in a phosphatidylcholine complex. Increased liver enzyme activity occurs commonly in dogs receiving Chloroethylcyclohexylnitrosourea (CCNU) chemotherapy (a nitrosourea alkylating agent used in veterinary medicine to treat a variety of canine cancers). Although most dogs do not develop hepatopathy to the degree that medical intervention is necessary, CCNU treatment may be delayed or discontinued to prevent potential liver failure. In this study, 50 dogs were prospectively randomized to receive either concurrent SAMe and silybin during CCNU chemotherapy (n = 25) or to receive only CCNU (n = 25). Serum biochemical profiles for hepatic parameters (ALT, AST, AP, bilirubin, and cholesterol) were analyzed before each dose of CCNU. Increased ALT activity occurred in 84% of dogs receiving CCNU alone (21 dogs) and in 68% of dogs on concurrent SAMe and silybin (17 dogs). Dogs receiving CCNU alone had significantly greater increases in ALT (P = .03), aspartate aminotransferase (P = .01), alkaline phosphatase (P = .009), and bilirubin (P = .02), and a significantly greater decrease in serum cholesterol concentrations (P = .02) than dogs receiving concurrent SAMe and silybin. Dogs receiving CCNU alone were significantly more likely to have treatment delayed or discontinued because of increased ALT activity. The authors suggested that SAMe and silybin can minimize the effects of CCNU on both hepatocellular damage and biliary dysfunction. The authors also objectively reported several weaknesses of their study: (1) the low number of cases that underwent additional liver testing with bile acids, abdominal ultrasound examination, and liver biopsies; (2) the low incidence of severe liver disease that may have affected results comparing changes between groups in blood urea nitrogen, albumin, cholesterol, and glucose levels, which are measures of liver function that change only when the organ is severely affected; (3) the lack of placebo in the control group, and lack of blinding of clinician as to which group each dog was assigned; (4) the occult preexisting liver disease in some dogs enrolled into the study, which may have affected results; and (5) the combination of 2 agents in the compound that was studied instead of individual products. The authors also had potential financial conflicts of interest.

**VITAMIN E**

Eight isomers (vitamers) of vitamin E exist, the most biologically active of which is α-tocopherol. Vitamin E is synthesized by plants and is found primarily in vegetable oils, nuts, seeds, and grains. Its primary physiologic role is as an antioxidant. Vitamin E is a lipid-soluble component of cell membranes that inhibits lipid peroxidation and modulates intracellular signaling pathways that rely on reactive oxygen intermediates. A dose of 15 IU/kg/d orally of α-tocopherol acetate has been recommended for dogs. No adverse effects have been reported although vitamin E may inhibit the absorption of other fat-soluble vitamins when administered at high doses. In veterinary medicine, vitamin E supplements have been recommended for dermatologic and hepatobiliary diseases (cholestatic and necroinflammatory hepatopathies) in which antioxidant activity may be of benefit. However, no scientific data support their use for any of these indications.
**N-ACETYL-CYSTEINE**

*N*-acetylcysteine (NAC) is a formulation of the amino acid *L*-cysteine that is an FDA-approved drug for specific indications in humans, specifically as a mucolytic agent (inhalation) and acetaminophen antidote (oral). NAC is also marketed as a nutritional supplement that may have hepatoprotective effects. NAC may be used to replenish intracellular cysteine and glutathione levels, which are important for overall hepatic health. Several other potentially hepatoprotective effects have been reported, including an effect on vascular tone that may improve oxygen delivery in acute liver failure, effects on hepatic mitochondrial energy metabolism, and potential effects on inflammation.

A study in which obstructive jaundice was produced by ligation of the common bile duct for 7 days in 2 groups of male beagle dogs (*n* = 14; receiving either 5% dextrose or NAC) suggested that NAC increased the concentrations of plasma cyclic 3′,5′-guanosine monophosphate (cGMP) (intracellular cGMP elicits vasorelaxant mechanisms and plasma cGMP concentrations may be related to hemodynamic alterations in patients with cirrhosis) serum and hepatic-reduced glutathione, and hepatic adenine triphosphate (ATP) (reduced hepatic ATP may demonstrate impaired energy homeostasis) in cholestatic-induced hepatopathy. In an in vivo canine liver model of ischemic reperfusion injury (*n* = 15), Baumann and colleagues evaluated NAC’s potential protective effects (150 mg/kg injected intravenously before induction of ischemia) as determined by indocyanine green plasma disappearance rate. Plasma clearance of indocyanine green and serum levels of AST and ALT showed no significant differences between NAC-treated and untreated groups.

**HEPATOACTIVE NUTRACEUTICALS: WHAT CAN BE GLEANED FROM AVAILABLE SCIENTIFIC LITERATURE?**

Currently, limited available evidence exists regarding the efficacy of nutritional supplements. Two reviews detail the use of dietary supplements as hepatoprotectants for dogs, but only 8 clinically relevant publications were referenced. Only under very limited circumstances were some nutritional supplements shown to have a favorable biochemical or clinical outcome in treating or preventing hepatic disease.

Minimal regulatory oversight of veterinary nutritional supplements may explain this lack of scientific evidence regarding the clinical efficacy of these products. Because the FDA does not consider nutritional supplements to be drugs, manufacturers are not currently required to provide efficacy data as long as the label does not make medicinal claims.

When evaluating the scientific literature available for nutritional supplements, one must consider the route of administration and composition of the compound used in the research population compared with the composition of the marketed product. In some research publications, a highly purified compound with verified potency was used rather than the commercially available nutritional supplement. Additionally, using multiple nutritional supplements makes it difficult to ascertain which particular compound may have provided a beneficial effect.

**SUMMARY**

Until greater regulatory oversight of nutritional supplements is required, veterinarians will have to weigh the costs, risks, and potential benefits of nutritional supplements for their patients on an individual basis. Veterinarians should strive to maintain a critical view of nonscientific promotional material and rely primarily on
scientific evidence. Before recommending or administering a nutritional supplement to canine patients with the intent of providing hepatoprotection, veterinarians should obtain informed consent from owners to ensure that they understand that little to no evidence exists to support the use of these products for treatment or prevention of liver disease. Veterinarians must also be aware that lack of adequate regulation of so-called nutraceuticals increases the risk of lack of quality control, labeling inaccuracies, and omission of cautionary statements. Although some dietary supplements have shown beneficial effects under limited in vitro conditions or for a very specific hepatotoxin, their general use as global hepatoprotectants remains questionable.

REFERENCES


