



## Potential Drug Interactions with Dietary Supplements

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### ABSTRACT:

Use of dietary supplements, including vitamins, minerals, nutraceuticals, and herbal remedies, is increasing in human and veterinary patients. As supplementation becomes more widespread, the potential for adverse interactions with prescribed medications increases. Dietary supplements may decrease the absorption of other drugs, inhibit or induce drug clearance, or exacerbate pharmacologic effects such as antiplatelet or anticoagulant activity. Research into clinically relevant drug–supplement interactions is expanding, but valid clinical data are still lagging behind dietary supplement use.

The term *dietary supplement* encompasses a broad range of products, including vitamins, minerals, herbs, and nutraceuticals.<sup>1,2</sup> In humans, concurrent use of dietary supplements and prescription medication is common. In 1997, approximately one of five patients taking prescription medication also took supplements, and most supplement users did not report supplement use to their health care providers.<sup>3</sup> In a recent study of veterans hospital patients,<sup>4</sup> almost half were taking at least one dietary supplement with a prescription medication. Among these, an adverse drug–supplement interaction was considered possible in 45%, with 6% having the potential for a severe interaction.<sup>4</sup>

Dietary supplements are often dispensed or purchased without medical supervision, and unlike FDA oversight of prescription and over-the-counter drugs, FDA oversight of dietary supplements is minimal. Manufacturers of dietary supplements intended for human use are not required to submit safety data before marketing their products, and

if a safety concern arises, the burden falls on the FDA to prove that the supplement is unsafe.<sup>1,3,5</sup>

*Dietary supplement* is a legal term referring only to human, not veterinary, products. However, human dietary supplements are often used in veterinary patients, and veterinary products containing similar constituents are marketed. Because supplements are prescribed for a variety of disorders, ranging from dull haircoat to liver failure, their use in veterinary medicine is common and increasing. Based on a survey conducted by Ralston Purina in 2000,<sup>6</sup> nearly 30% of pet owners have used or considered using supplements for their pets. The widespread use is reflected in market research. According to a recent report<sup>7</sup> released by Business Communications Company, pet supplement sales are predicted to reach at least \$1 billion by 2005, and growth is projected at 17% to 22%. Because supplements are often recommended for managing conditions that also require prescription medications, the risk of potential drug–supplement interactions is also present in veterinary patients.

Because many supplements are marketed as “all natural,” pet owners may assume that they

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are safe and fail to mention using them to veterinarians. Conversely, veterinarians may not ask specifically about supplement use before prescribing new medications. Veterinarians should be prepared to advise owners regarding possible drug interactions with vitamins, minerals, herbs, and nutraceuticals. Because virtually no research has been done in veterinary patients, the risk of interactions must be based primarily on what is known from humans and experimental animal models.

## VITAMINS

Vitamins are a group of compounds that are essential in small amounts for normal metabolism.<sup>8</sup> They serve as cofactors for various enzyme systems and can be categorized as water-soluble (i.e., vitamin C and B vitamins) or fat-soluble (i.e., vitamins A, D, E, and K) based on their chemical properties and metabolic fate.<sup>8</sup>

$\alpha$ -Tocopherol (i.e., vitamin E) is one of the most important lipid-soluble antioxidants and functions to inhibit cell membrane lipid peroxidation.<sup>8,9</sup> In veteri-

nitamin E supplementation in veterinary patients suspected of having a vitamin K-dependent coagulopathy should be based on strong rationale and monitored carefully. In addition, vitamin E supplementation should be avoided in patients treated with, or exposed to, warfarin or related anticoagulant rodenticides.

## MINERALS

Minerals such as calcium, phosphorus, potassium, magnesium, and iron are inorganic elements that are important for various physiologic functions. Minerals act as structural components of tissues, electrolytes in body fluids, and catalysts and cofactors in enzymatic reactions.<sup>8</sup> Quite a few clinically relevant mineral-drug interactions have been reported in humans.

### Multivalent Cations

Divalent or multivalent cationic minerals such as calcium, iron, and zinc are found in multivitamins; aluminum is found in antacids, phosphate binders, and

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nary medicine, vitamin E supplementation is commonly prescribed for dermatologic and hepatobiliary disorders. Recommended doses for dogs and cats range from 10 to 100 IU/kg/day, depending on the reason for supplementation.<sup>9</sup>

Vitamin E has a potentially serious adverse interaction with anticoagulants. Overdoses of vitamin E alone can lead to coagulopathy,<sup>10</sup> and even modest doses (e.g., 1,000 IU/day [approximately 15 IU/kg/day] in humans) can lead to subclinical decreases in the function of prothrombin, a vitamin K-dependent coagulation factor.<sup>11</sup> Although the exact mechanism is not understood, it is hypothesized that high-dose vitamin E may antagonize the effects of vitamin K.<sup>11</sup> Vitamin E has been shown to exacerbate the anticoagulant effect of warfarin<sup>11,12</sup>; dogs administered warfarin and supplemented with 400 IU vitamin E/day developed a profound coagulopathy that was not present in dogs administered warfarin alone.<sup>13</sup> Until more is known,

sucralfate. Each of these minerals can interact with orally administered drugs via chelation or adsorption,<sup>14</sup> rendering drugs unavailable for systemic absorption and reducing their efficacy. Drugs that are significantly affected by chelation with multivalent cations include fluoroquinolones, tetracycline, doxycycline, and penicillamine<sup>14-17</sup> (Table 1). For example, when ciprofloxacin is given concurrently with aluminum- or magnesium-containing antacids in humans, the bioavailability of ciprofloxacin is only 15%.<sup>18</sup> Even when ciprofloxacin is given 2 hours after the antacid, its relative bioavailability is only 23%.<sup>18</sup> However, giving ciprofloxacin first, followed by the antacid 2 hours later, does not adversely affect antibiotic bioavailability.<sup>18</sup> Although comparable studies have not been conducted in dogs and cats, similar interactions would be expected for fluoroquinolones and antacids, phosphate binders, or sucralfate in veterinary patients.

Calcium and other cations are known to interfere with

**Table 1. Mineral Interactions with Prescription Drugs**

Drug(s)	Interacting Mineral(s)	Outcome
Fluoroquinolones	Aluminum Iron Magnesium Calcium Zinc	Decreased absorption of fluoroquinolone, unless the antibiotic is given at least 2 hours <i>before</i> the cationic mineral
Tetracycline Doxycycline	Calcium Aluminum Zinc Magnesium Iron	Decreased absorption
Penicillamine	Iron	Decreased absorption
Thyroxine	Calcium	Decreased serum T <sub>4</sub> concentrations in humans
Bromide	Dietary chloride	Enhanced bromide elimination Decreased serum bromide concentrations
ACE inhibitors Spironolactone	Potassium	Possible hyperkalemia

tetracycline and doxycycline absorption.<sup>19</sup> Calcium also adsorbs orally administered thyroxine in the acid environment of the stomach, leading to impaired control of hypothyroidism in humans.<sup>20</sup> Although studies in dogs have not been conducted, it is possible that the same adsorption interaction occurs. It may be advisable to administer thyroxine at least 2 hours before calcium-containing drugs or consistently with or without food to ensure steady bioavailability in dogs. Similar thyroxine bioavailability studies have not been conducted with other cationic minerals such as zinc, aluminum, or iron.

### Electrolytes

Mineral electrolytes such as chloride and potassium can also interact with drugs. The most marked example of this is the interaction between the anticonvulsant bromide and dietary chloride in dogs.<sup>21,22</sup> Bromide and chloride are both halide anions that are distributed and eliminated through similar mechanisms. These anions compete for renal resorption, and high chloride intake has been shown to increase bromide elimination.<sup>23</sup> In dogs, a sixfold increase in dietary chloride intake markedly shortens the elimination half-life of bromide and leads to a pronounced decrease in predicted steady-state serum bromide concentrations.<sup>22</sup> This has been observed clinically when a change to a higher chloride

diet has been associated with marked decreases in serum bromide concentrations and subsequent increases in seizure activity.<sup>21</sup> Dogs administered high-chloride diets, salt supplements, or chloride-containing fluids or drug formulations would be expected to have lower serum bromide concentrations compared with dogs not receiving supplemental chloride. In these cases, the effect of bromide on seizure control is likely to be diminished. In addition, in dogs fed high-chloride diets, higher maintenance doses of 50 mg/kg/day or more may be necessary to

maintain serum bromide concentrations in the therapeutic range.<sup>21</sup>

Another potential mineral electrolyte–drug interaction exists between potassium supplementation and patients receiving spironolactone or angiotensin-converting enzyme (ACE) inhibitors. Spironolactone and ACE inhibitors may cause hyperkalemia because of a direct or indirect decrease in aldosterone activity.<sup>24,25</sup> Mild hyperkalemia develops in approximately 10% of humans after prescription of an ACE inhibitor and is most common in patients with specific risk factors, including impaired renal excretion of potassium, concurrent use of an ACE inhibitor and a potassium-sparing diuretic, and potassium supplementation.<sup>26</sup>

Potassium supplementation is commonly indicated in veterinary patients; approximately 20% to 30% of cats with chronic renal failure are hypokalemic at presentation.<sup>27</sup> Although documented clinical reports in companion animals are lacking, potassium supplementation in veterinary patients also receiving an ACE inhibitor or spironolactone may increase the risk of hyperkalemia. Consequently, serum potassium levels should be monitored in cats or dogs receiving potassium supplementation with ACE inhibitors or spironolactone because dose adjustments in potassium supplementation may be indicated.

## NUTRACEUTICALS

A legal definition for the term *nutraceutical* has not been established.<sup>28</sup> The North American Veterinary Nutraceutical Council defines a nutraceutical as a “non-drug endogenous substance that is produced in a purified or extracted form and administered orally to provide agents required for normal body structure and function with the intent of improving the health and well-being of animals.”<sup>28,29</sup> In other words, nutraceuticals are substances that have characteristics of both foods and drugs.

### S-Adenosylmethionine

S-Adenosylmethionine (SAME) is frequently used in veterinary medicine for its antioxidant properties, especially in cases of liver disease. It is an indirect precursor to glutathione, a major cellular antioxidant. In companion animals, hepatic glutathione depletion occurs in

rather weak. Although the potential exists for SAME to interact with imipramine, clomipramine, or amitriptyline, there is currently no veterinary documentation of this interaction.

### Glucosamine and Chondroitin

Glucosamine and chondroitin supplements have been advocated in treating osteoarthritis because of their purported mild antiinflammatory properties and ability to stimulate proteoglycan synthesis and inhibit degradative enzymes associated with osteoarthritis.<sup>39</sup> Controlled clinical trials of glucosamine in humans with osteoarthritis have shown both positive and negative results<sup>40–43</sup>; one controlled study in dogs showed no clinical improvement over a placebo.<sup>44</sup>

Early studies suggested that parenterally administered glucosamine was associated with insulin resistance when

## Many herbs have antiplatelet or anticoagulant activity.

inflammatory liver disorders, extrahepatic biliary duct obstruction, and feline hepatic lipidosis.<sup>30</sup>

SAME readily crosses the blood–brain barrier and has been shown in humans to have antidepressant activity.<sup>31–33</sup> Although the exact mechanism by which SAME supplementation affects mood regulation is unclear, SAME-dependent methylation reactions are required for both synthesis and inactivation of neurotransmitter monoamines such as dopamine and serotonin.<sup>34</sup> Low SAME concentrations have been found in the cerebrospinal fluid of clinically depressed patients.<sup>35</sup> Conversely, a positive correlation exists between increased plasma SAME concentrations and decreased clinical signs of depression.<sup>36</sup> Use of SAME to regulate mood or behavior in veterinary patients has not been explored.

Potential interactions between SAME and tricyclic antidepressants have been described. In mouse studies,<sup>37</sup> treatment with a single dose of imipramine temporarily causes a 50% decrease in brain SAME concentrations and chronic treatment with imipramine causes a similar but long-lasting decrease in brain SAME levels. In other clinical studies,<sup>32</sup> imipramine has a faster onset of action when given with SAME. A human case report<sup>38</sup> suggests that combination of SAME and clomipramine led to development of serotonin syndrome (i.e., tremors, gastrointestinal upset, motor restlessness) in a patient. However, the evidence provided in this case report was

administered at doses 100- to 1,000-fold higher than those used in clinical practice.<sup>45</sup> This raised the concern that glucosamine supplementation in diabetics could lead to poor glycemic control. However, glucosamine infused at clinically relevant doses in healthy human subjects did not affect insulin sensitivity or plasma glucose concentrations.<sup>46,47</sup> In addition, there is no effect on glycosylated hemoglobin levels in humans with well-controlled type 2 diabetes after 90 days of oral glucosamine supplementation.<sup>48</sup> Therefore, a clinically relevant interaction between glucosamine and insulin or glycemic control appears unfounded in humans. Although studies in diabetic dogs and cats have not been conducted, oral glucosamine supplementation does not affect plasma glucose concentrations in healthy dogs.<sup>49</sup>

### Shark Cartilage

Shark cartilage has been thought to benefit cancer patients by preventing tumor growth and metastasis.<sup>50,51</sup> Use of crude shark cartilage supplements to treat cancer in humans remains controversial because of unsatisfactory patient outcome in clinical trials and lack of data correlating bioavailability to pharmacologic effects.<sup>52,53</sup> Although purified substances from shark cartilage may antagonize tumor angiogenesis,<sup>54,55</sup> there is no clear evidence that crude shark cartilage supplementation in companion animals would result in clinical benefits.

Because shark cartilage preparations contain large amounts (i.e., up to 25% in some products) of calcium salts, hypercalcemia is a potential consequence of crude shark cartilage supplementation.<sup>50</sup> Although no veterinary reports have been published, human case reports have documented hypercalcemia secondary to use of shark cartilage supplements, especially when given with multivitamins containing calcium and vitamin D.<sup>56</sup> Because of its high calcium content, crude shark cartilage may interfere with tetracycline, doxycycline, and thyroxine absorption.

### **Omega-3 Fatty Acids**

Omega-3 fatty acids are frequently used in veterinary medicine to treat dermatologic conditions, protein-losing nephropathies, hyperlipidemia, and degenerative joint disease. In human medicine, their uses also include managing hypertension and preventing cardiovascular disease.<sup>50</sup> Omega-3 fatty acids are thought to reduce platelet activation and lower plasma levels of coagulation factors.<sup>57</sup> No additive effects on platelet inhibition have been identified in healthy humans concurrently

cylates, cardiac glycosides, warfarin, and morphine.<sup>62,63</sup> Despite the long history of herbal medicine, pharmacokinetic and pharmacodynamic information about herbal remedies is largely lacking.<sup>64</sup>

Because dietary supplements are not required to undergo premarket approval regarding labeling claims, product labels may contain little information about specific concentrations of ingredients. Most herbal extracts contain multiple components, and the concentrations of active compounds, if characterized, can vary greatly, depending on the plant source, season of harvest, and method of extraction. Consequently, batches of products may vary considerably in the quantity of the active ingredient; in some products, the active ingredient is completely absent. For example, of 24 ginseng products analyzed by a thin-layer chromatography spectrophotometric method, 33% did not contain detectable levels of ginseng's active component.<sup>65</sup> In addition, some herbal products are contaminated with heavy metals or contain unlabeled ingredients, including drugs such as acetaminophen, ephedrine, and caffeine.<sup>66</sup> Therefore, interactions between herbs and prescription drugs are much

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## **The American Society of Anesthesiologists recommends that patients discontinue all herbal medications 2 to 3 weeks before elective surgical procedures.**

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taking acetylsalicylic acid and omega-3 fatty acid supplementation.<sup>58</sup> However, several human reports document prolonged coagulation times after adding omega-3 fatty acids to a warfarin regimen.<sup>59,60</sup>

Omega-3 fatty acid supplementation may also affect the bioavailability of lipophilic drugs such as cyclosporine. A pharmacokinetic study involving human renal transplant patients taking both cyclosporine and omega-3 fatty acids identified a larger cyclosporine area under the curve with a higher blood peak level compared with those not taking the omega-3 fatty acid supplement.<sup>61</sup> This translates to greater cyclosporine absorption and possibly better bioavailability in patients taking both cyclosporine and omega-3 fatty acid supplementation.

### **HERBAL REMEDIES**

Herbal medicine has been practiced for thousands of years and has given rise to important drugs such as sali-

more difficult to consistently predict than are interactions between prescription drugs themselves.

Although interest in clinical studies evaluating herb-drug interactions has recently increased, most available information is still based on individual case reports, in vitro enzymatic data, and rodent studies. Examples of potential herb-drug interactions are listed in Table 2. Because of the widespread use of herbal supplements along with prescription drugs in both humans and veterinary patients, continued research is needed to further assess the clinical significance of these interactions.

### **St. John's Wort**

The strongest evidence for clinically important drug-herb interactions exists for St. John's wort (*Hypericum perforatum*), which is used to treat mood disorders in humans.<sup>67</sup> In Germany, St. John's wort is marketed and regulated as a drug. In the United States, it is avail-

able over the counter and is even formulated in numerous veterinary products, some of which also contain valerian, German chamomile, and kava kava. St. John's wort has proven clinical efficacy for mild to moderate depression in humans,<sup>68</sup> although its mechanism of action is debated. It inhibits isoforms of monoamine oxidase in vitro and, at high concentrations, prevents reuptake of neurotransmitters such as serotonin, norepinephrine, and dopamine. However, inhibition of  $\gamma$ -aminobutyric acid receptors may best explain its antidepressant activity.<sup>68</sup> Because of the mechanistic effects of St. John's wort on neurotransmitters, adverse interactions have been reported when the herb is used with other psychoactive drugs. For example, this herb has been associated with serotonin syndrome when administered with sertraline or buspirone in humans.<sup>69</sup>

St. John's wort increases the expression of intestinal P-glycoprotein, which is important for the excretion of many drugs.<sup>70</sup> It also induces expression of CYP3A4 (a cytochrome P450 enzyme responsible for clearance of a large number of prescription drugs, some of which are also P-glycoprotein substrates) and CYP1A2, which is responsible for theophylline and warfarin metabolism. There is considerable evidence that repeated dosing of St. John's wort decreases plasma concentrations of several P-glycoprotein, CYP3A4, or CYP1A2 substrates, including cyclosporine, fexofenadine, midazolam, digoxin, tacrolimus, amitriptyline, warfarin, and theophylline.<sup>69,71,72</sup> St. John's wort has been associated with a loss of cyclosporine efficacy and subsequent graft rejection in patients following heart, liver, or kidney transplantation.<sup>69</sup> Although no studies have been conducted in veterinary patients, St. John's wort may lead to decreased efficacy of many drugs in dogs and cats. These potential interactions require study.

### Milk Thistle

Milk thistle has been used as a hepatoprotectant and to enhance liver regeneration. The active component in milk thistle, silymarin, consists of three biologically

active flavonoids.<sup>9,73</sup> Milk thistle is thought to provide antioxidant effects, accelerate hepatocellular regeneration, and mitigate the severity of hepatic fibrosis.<sup>9</sup> Its antifibrotic effects are due to inhibition of both Kupffer cells<sup>74</sup> and TNF- $\alpha$ , causing decreased expression of various genes involved in inflammation.<sup>75</sup> The antifibrotic effects of milk thistle are comparable with those of colchicine in some animal models.<sup>9,76</sup>

Evidence suggests that silymarin can suppress the activity of certain cytochrome P450 enzymes.<sup>73,77</sup> Although the possibility of altered drug metabolism exists, little is known regarding the drug interaction potential of milk thistle. Further research is necessary to fully evaluate the effect of silymarin on the metabolism of other drugs.

### Ginkgo

Ginkgo biloba is one of the most popular herbal products available in the United States<sup>3</sup> and has been shown to improve cognitive function in healthy humans and those with dementia.<sup>78,79</sup> These effects have been

**Table 2. Potential Herb–Drug Interactions**

Herb	Interacting Drugs	Result
St. John's wort	Cyclosporine Fexofenadine Midazolam Digoxin Tacrolimus Amitriptyline Warfarin Theophylline	Decreased plasma drug concentrations
	Sertraline Buspirone	Serotonin syndrome
Ginkgo	Warfarin Heparin NSAIDs	Bleeding
	Omeprazole	Decreased plasma concentrations
Ginseng	Warfarin Heparin NSAIDs	Bleeding Falsely elevated serum digoxin levels (laboratory test interaction with ginseng)
	Opioids	Decreased analgesic effect Falsely elevated serum digoxin levels (laboratory test interaction with ginseng)
Garlic Chamomile Ginger Others	Warfarin Heparin NSAIDs	Bleeding

## Resources

### ConsumerLab.com

Information on label validation of specific herbal remedies

### www.fda.gov

Adverse event reporting system for dietary supplements taken by humans

attributed to increased cerebral blood flow<sup>80</sup> and restoration of normal mitochondrial function.<sup>81</sup> Ginkgo has been advocated for treating canine cognitive dysfunction and is even available in Nylabone Health Supplement Edible Chew Bones with Ginkgo Biloba (Nylabone Products, Neptune City, NJ) for dogs.

Ginkgo can enhance bleeding in susceptible patients. Ginkgolide B, one of the constituents of ginkgo, inhibits binding of platelet-activating factor to its receptors on platelet membranes and results in reduced platelet aggregation.<sup>3,82</sup> A study of human volunteers found marked inhibition of platelet aggregation after single doses of mixed ginkgolides.<sup>82</sup> In addition, several case reports<sup>83,84</sup> have documented spontaneous hemorrhage attributed to ginkgo supplementation. Because of the effects of ginkgo on platelet function in humans, concomitant use of ginkgo with NSAIDs and anticoagulants such as heparin is not recommended.

Ginkgo biloba also appears to be a cytochrome P450 inducer, specifically in humans, of CYP2C19, which metabolizes drugs such as diazepam, imipramine, and omeprazole. When used for approximately 2 weeks, ginkgo reduced plasma concentrations of omeprazole by up to 50%,<sup>85</sup> which would be expected to decrease the antacid efficacy of omeprazole. Conversely, ginkgo may inhibit other cytochrome P450s (e.g., CYP3A4 in humans) as well as intestinal P-glycoprotein. In rodents, this inhibition led to increased plasma concentrations of the calcium channel blocker diltiazem.<sup>64</sup>

## Ginseng

Several types of ginseng are marketed in the United States: American ginseng, Asian ginseng, and Siberian ginseng/eleuthero.<sup>3</sup> Each variety has been advocated for boosting the immune system and enhancing stamina. Ginseng is an ingredient in several veterinary products.

Components of Asian ginseng inhibit platelet aggregation via altered calcium influx, antagonism of platelet-activating factor, and decreased thromboxane A<sub>2</sub> produc-

tion.<sup>86,87</sup> A few case reports<sup>88-90</sup> have associated bleeding with ginseng intake, but those involving vaginal bleeding may have been caused by estrogenic effects of ginseng rather than platelet dysfunction.<sup>91</sup> There are no clinical data documenting an interaction between ginseng and NSAIDs; however, some investigators recommend against using ginseng in combination with NSAIDs, warfarin, or heparin.<sup>3,92</sup>

Interestingly, ginseng has been shown to reduce the analgesic effect of opioids.<sup>3</sup> The mechanism for this interaction is unknown. Siberian ginseng has also been associated with falsely elevated digoxin serum levels in the absence of clinical digoxin toxicity, presumably due to interference by ginseng constituents with the digoxin assay.<sup>92,93</sup>

## Other Herbs with Potential Anticoagulant Interactions

Quite a few herbs have anticoagulant activity. This is not surprising given that both warfarin and salicylate were originally derived from herbs.<sup>62</sup> Garlic is advocated in humans to improve cardiovascular function and is also marketed as a flea repellent for pets. Garlic derivatives inhibit aggregation of both human and canine platelets *in vitro*,<sup>94</sup> and garlic supplementation has been associated with bleeding in humans in several case reports.<sup>95</sup> Chamomile is recommended as a mild sedative and antispasmodic<sup>3,92</sup> and is marketed to pet owners in various products. Chamomile reportedly contains coumarin. However, despite widespread use of chamomile in humans, no cases of bleeding have been reported.<sup>3,92</sup> Ginger has been recommended empirically for travel-related nausea in dogs and cats. It is effective in humans for morning sickness related to pregnancy.<sup>96</sup> Ginger is an inhibitor of thromboxane synthetase (i.e., cyclooxygenase 1) activity, and its constituents show more potent antiplatelet effects *in vitro* than even aspirin.<sup>97</sup> One case report<sup>98</sup> suggests an interaction between warfarin and ginger in humans. Although information is still inadequate, garlic, chamomile, ginger, and other herbs have the potential to augment the effects of NSAIDs, heparin, and other prescription drugs with anticoagulant activity.<sup>3,99</sup> Because of the potential for adverse herb-drug interactions, the American Society of Anesthesiologists recommends that all herbal medications be discontinued 2 to 3 weeks before elective surgical procedures.<sup>99</sup>

## CONCLUSION

Use of supplements, including vitamins, minerals, herbs, and nutraceuticals, is increasing in veterinary

medicine. The decision to recommend a supplement may be based on laboratory data (as in hypokalemic patients), mainstream practices (such as prescribing vitamin E to improve haircoat quality), or empirical beliefs of potential benefits. Regardless, even veterinarians who do not advocate alternative medicine will find it increasingly difficult to avoid the topic of supplementation. Based on the limited knowledge available today, the potential for clinically relevant interactions exists between commonly used supplements and frequently used veterinary drugs. Consequently, knowledge of potential supplement–drug interactions is a necessity.

Although the FDA has created an adverse event reporting system for dietary supplements taken by humans, no equivalent nonbiased reporting system exists for veterinary supplements or for veterinary patients receiving supplements marketed for humans. Consequently, the National Animal Supplement Council (NASC), a nonprofit industry association, created an adverse event reporting system in 2003.<sup>2</sup> Members of the NASC are required to investigate and enter reports of adverse events related to their product on a monthly basis. Although the database is available only to NASC members and the data are confidential, the database is the largest reporting system available, and the information is made available to the FDA.

More research is needed to fully understand the implications of drug–supplement interactions in veterinary patients. Observations in the clinic are essential in directing future research. If interactions are not observed or reported to product manufacturers or other organizations, such as the Animal Poison Control Center, or even in veterinary journals, veterinary knowledge of supplement–drug interactions will be significantly impaired.

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## ARTICLE #4 CE TEST

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### 1. Which statement regarding dietary supplements is false?

- a. No legal definition exists for the term *nutraceutical*.
- b. The FDA provides an adverse event reporting system that recognizes animal supplement–drug interactions.
- c. Manufacturers of supplements intended for human use do not need to submit safety data before marketing their product.
- d. Nutraceuticals have characteristics of both foods and drugs.

### 2. High doses of vitamin E are thought to

- a. antagonize the action of vitamin K, thereby causing vitamin K–dependent coagulopathy.
- b. antagonize the action of warfarin, thereby decreasing its effectiveness.
- c. have antiplatelet actions.

- d. increase circulating levels of prothrombin, a vitamin K–dependent coagulation factor.

### 3. Which drug is not affected by chelation or adsorption interactions with multivalent cations?

- a. thyroxine
- b. fluoroquinolones
- c. itraconazole
- d. doxycycline

### 4. In human studies, if ciprofloxacin is given at the same time as an aluminum- or magnesium-containing antacid, the bioavailability is

- a. 15%.
- b. 25%.
- c. 50%.
- d. 75%.

**5. Which anion interacts with the anticonvulsant bromide?**

- a. chloride
- b. sodium
- c. potassium
- d. calcium

**6. Which statement regarding SAME is false?**

- a. It is an indirect precursor to glutathione.
- b. It is an antioxidant.
- c. It is used as an antidepressant in human medicine.
- d. It cannot cross an intact blood–brain barrier.

**7. Which is(are) not an effect of glucosamine and chondroitin?**

- a. mild antiinflammatory effects
- b. stimulation of proteoglycan synthesis
- c. insulin resistance at clinical doses
- d. inhibition of degradative enzymes associated with osteoarthritis

**8. Which herb does not interact with cytochrome P450 enzymes?**

- a. St. John's wort
- b. ginkgo
- c. ginseng
- d. milk thistle

**9. Which herb does not have anticoagulant effects?**

- a. ginkgo
- b. milk thistle
- c. ginseng
- d. chamomile

**10. Which statement regarding dietary supplements is false?**

- a. Shark cartilage may decrease the absorption of doxycycline if given concurrently.
- b. Omega-3 fatty acids and acetylsalicylic acid have been shown to have additive effects on platelet inhibition.
- c. Siberian ginseng interferes with the digoxin assay, causing false digoxin elevations.
- d. Warfarin and salicylate were originally derived from herbs.