Supplements for Exotic Pets

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KEYWORDS

• Alternative medicine • Supplements • Exotic pet • Herbal • Nutritional

KEY POINTS

- Animals have been choosing specific medicinal plants to treat their own diseases for as long as we can surmise. The practice of Zoopharmacognosy is discussed in detail showing that supplementation with plants has historically been documented in the wild.
- Dietary supplements are not as strictly regulated under the United States Food and Drug Administration (FDA) as prescription and over-the-counter drugs. Therefore, reputable nutraceutical companies should be committed to abiding by good manufacturing practices, choosing to work under accredited third-party certification providers.
- Vision, liver, immune, and stress supplement support are discussed because there is increasing scientific evidence of the effectiveness of these supplements in exotic species.
- It is increasingly important for the exotic animal practitioner to become knowledgeable about the various forms of complementary supplementation and research.

INTRODUCTION

This article discusses how practitioners can use nutritional and herbal supplements to support the health of exotic patients. Packaged Facts reported in 2013 that "a large share of non-dog/cat population are fish at 84.2 million, followed by birds at 11.4 million, reptiles at 3.9 million, followed by a range of other pets, including 5 million rabbits and hamsters."[1] Natural and organic pet foods, pet supplements, and other natural and organic pet supplies grew 5.2% in 2010 to reach $3.2 billion, with the animal supplement category adding $80 million in new sales to reach $1.6 billion.[2] If the most common diseases that affect exotic species are understood, then clinicians can try to prevent or alleviate disease states by providing supplements that both protect and support organ systems.

Disclosure: Dr J. Mejia-Fava is co-owner of Animal Necessity, LLC, a company that produces supplements for use in animals, some of which are discussed in this article.

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Although it is accepted that food adaptations are critical to the survival of every species, it is not as readily apparent that food can also be purposefully used by animals for medicinal purposes. Zoopharmacognosy is the study of the ability of animals to recognize medicinal plants and other substances, and to ingest or otherwise apply them to their bodies to help prevent or treat disease.[3–5] Observations of animals healing themselves with natural medicinal foods have been recorded since ancient times.[3–5] Some herbs such as dog grass (*Agropyron repens*), catnip (*Nepeta cataria*), and horny goat weed (*Epimedium* spp) still carry the common names of the species using them medicinally. The term zoopharmacognosy was coined by Dr Eloy Rodriguez, a biochemist and professor at Cornell University.[5] This principle was popularized in 1987, when researchers investigated animals in the wild that were self-medicating by using the medicinal properties of plants, soils, clays, fungi, and insects.[5] Chimpanzees with diarrhea were confirmed to have intestinal parasitism with *Oesophagostomum stephanostomumto*.[5] Twenty hours after eating the pith of the *Vernonia* tree, one female's fecal excretion had lower levels of parasitism. Vernonioside B1, a compound isolated from the pith, was found to possess antiparasitic, antitumor, and antibacterial properties.[5] Other research shows that chimpanzees eat *Aspilia* leaves for their antiparasitic properties during the rainy season, because this is when parasitic larvae abound and there is increased risk of infection. The leaves are swallowed whole because they contain an oil called thiarubrine A, a compound that may decrease the ability of parasites to adhere to the intestinal wall.[4,5] The leaves also have unique Velcro-like hairs to which worms attach after passing through the digestive tract.[5] Humans use the *Aspilia* plant for a wide variety of diseases such as malaria, rheumatism, sciatica, and scurvy.[5] Other animals have used remedies for reproduction. African elephants seek a particular tree of the *Boraginaceae* family at the end of their gestation to induce labor.[5] The leaves and bark induce uterine contractions; pregnant Kenyan woman drink them in a tea to induce labor or abortion.[5] Fur rubbing has been observed in primates and bears that coat their fur with masticated plant materials as an insect repellant.[5] More than 200 species of songbird have a behavior called anting, in which they crush ants and rub them into their plumage. These crushed ants release formic acid, which is harmful to feather lice.[5]

Herbivorous and omnivorous mammals, birds, reptiles, and insects consume soil, stone, clay, and rock for medicinal purposes. The act of geophagy has been linked to alleviating diseases of the gastrointestinal tract (GIT).[3–5] Giraffes eat clay-rich termite mound soil for its detoxifying and absorptive properties. One clay mineral found in termite soil is kaolinite, which is the principal ingredient in the commercially available antidiarrheal drug, bismuth subsalicylate (Kaopectate).[5] Other reasons why animals use geophagy may be as a means to maintain proper gut pH, as a way to meet nutritional requirements, and to use sodium to detoxify secondary metabolites from consumed plants.[5] Dusky-footed wood rats have been observed to fumigate their nests by making tears in bay leaves, which release fumigating vapors that significantly reduce parasite survival.[5] Dogs commonly show plant-eating behaviors that are presumed to address a dietary deficiency of fiber, which has beneficial effects on energy metabolism, fecal characteristics, and digestive transit time.[6] The behavior of dogs eating grasses and then vomiting has been interpreted as both self-medication for gastrointestinal distress and as a form of relieving gas pressure in the stomach.[6] Cape foxes intentionally eat grass during periods of starvation to maintain digestive function.[6]

Another form of zoopharmacognosy is sponge carrying by Shark Bay dolphins of Australia. In one study, 5 sponge-carrying dolphins were found to be either solitary females, or females with dependent calves. All of these dolphins were healthy and reproduced successfully.[7] These sponges were surmised to be a natural marine product with antibacterial, antifungal, cytotoxic, and antimitotic properties.[7] Sponges contain spicules made of calcium carbonate, silica, and spongin (a natural type of collagen protein similar to keratin).[8] The study mentioned difficulty observing dolphins ingesting the sponges; perhaps the dolphins were not ingesting sponges but exploiting a compound in the sponges they carried.[7] During their prenatal and postnatal periods, sponge ingestion may have been a natural mechanism to achieve increased calcium levels in dolphins.

Zoopharmacognosy has enhanced clinicians' ability to better supplement exotic patients. Exotic animals under human care are blocked from using wild, natural dietary components. The exotic pet owner must therefore provide all of the nutrients that the animal needs, making knowledgeable dietary supplementation a cornerstone of lifetime wellness.

IS IT ALTERNATIVE MEDICINE OR TRADITIONAL/ORIGINAL MEDICINE?

Many private exotic specialty practices use at least one form of alternative medicine for their patients. However, the literature is lacking on the topic of supplement use in exotic species. Most of the current knowledge is extrapolated from human and small animal medicine. Therapeutic practices that incorporate supplements are described as holistic, integrative, and/or complementary and alternative medicine (CAM). The National Center for Complementary and Alternative Medicine[9] classifies CAM into different categories including mind-body medicine (acupuncture, meditation), body-based practices (chiropractic manipulation, massage), energy medicine (Reiki, therapeutic touch), whole medicine systems, and biologically based practices.[9,10]

As an exotic animal practitioner and also both a formulator and consumer of natural products, one of the authors (JMF) has extensive personal experience with the use of nutritional and herbal supplements. The author agrees that "…in order to authentically criticize (either positively or negatively) any 'alternative' modality, the practitioner must have tried it in a clinical environment and/or for personal use. This, of course, presupposes that the practitioner has versed him/herself in the modality with sufficient study to apply it in an appropriate manner."[11]

This article focuses on biologically based practices (nutritional and herbal supplements) used in exotic species (**Boxes 1–4**).

REGULATION

Dietary supplements are not as strictly regulated under the United States Food and Drug Administration (FDA) as prescription and over-the-counter drugs.[27] Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the manufacturer is responsible for ensuring that the supplement is safe before it goes to market.[27] Supplements are not considered a drug and therefore are not intended to treat, diagnose, mitigate, prevent, or cure diseases. Reputable nutraceutical companies committed to abiding by good manufacturing practices voluntarily choose to work under accredited third-party certification providers. These certification providers allow stakeholders (industry, regulators, users, and the general public) to determine compliance with regulatory specifications, correct label claims and packaging, and proper quantity and purity of ingredients. These providers include the National Animal Supplement Council, Natural Product Association, Natural Safety Foundation, ConsumerLab, and US Pharmacopeial Convention. These certifications are not mandatory;

Box 1
Avian nutritional supplements and dosages

Agent	Dosage	Species
ALA	250 mg/kg of diet[12]	Japanese quail
Calcium	3–10 mg/kg feed (0.3–1%)[13]	Laying parrots
Essential fatty acids	0.5 mL/kg PO q 24 h × 50 d or indefinitely[13]	Raptors
Fatty acids (omega-3, omega-6)	0.1–0.2 mL/kg of flaxseed oil to corn oil mixed at a ratio of 1:4 PO or added to food; ratio of omega-6/omega-3 is 4–5:1[13]	Psittacines and pigeons
Fatty acids (omega-3, omega-6)	0.11 mL/kg q 24 h in a 5:1 ratio of omega-3[13]	Psittacines
Iodine (Lugol iodine)	0.2 mL/L drinking water daily[13]	Most bird species
	2 parts iodine + 28 parts water; 3 drops into 100 mL drinking water[13]	Budgerigars
Iodine (sodium iodide 20%)	2 mg (0.01 mL)/bird IM prn[13]	Budgerigars
	60 mg (0.3 mL)/kg IM[13]	Most bird species
Lactobacillus (Bene-Bac, Pet-Ag)	1 pinch/d/bird[13]	Psittacines
	1 tsp/L hand-feeding formula[13]	Most bird species
Pancreatic enzyme powder (Viokase-V Powder, Fort Dodge)	2–5 g/kg[13]	Most bird species
	1/8 tsp/kg feed[13]	Most bird species
	1/8 tsp/60–120 g lightly oil-coated seed[13]	Most bird species
Vitamin A (Aquasol A Parenteral, Astra)	5000 IU/kg IM q24h × 14 days, then 250–1000 IU/kg q 24h PO[13]	Psittacines
Vitamin B_1 (thiamine)	1–2 mg/kg PO q 24 h[13]	Raptors, penguins, cranes
	25–30 mg/kg fish (wet basis)[13]	Piscivorous species
Vitamin B_{12} (cyanocobalamin)	0.25–0.5 mg/kg IM q 7 d[13]	Most bird species
	2–5 mg/bird SC[13]	Pigeons
Vitamin C (ascorbic acid)	20–50 mg/kg IM q 1–7 d[13]	Most bird species
	150 mg/kg PO q 24 h[13]	Willow ptarmigan chicks
Vitamin D_3 (Vital E-A + D, Schering)	3300 IU/kg (1000 U/300 g) IM q7d prn[13]	Most bird species
	6600 IU/kg IM once[13]	Most bird species
Vitamin E (Vitamin E20, Horse Health Products; Bo-SE, Schering Plough)	0.06 mg/kg IM q 7 d[13]	Psittacines
Vitamin E/γ- linolenic acid (2%), linoleic acid (71%)(Derm Caps, DVM Pharmaceuticals)	0.1 mL/kg PO q 24 h[13]	Most bird species
	4000 mg linolenic acid/kg feed[13]	Japanese quail
Policosanol	0.3–2.0 mg/kg orally[14]	Most bird species
Melissa or lemon balm (*Melissa officinalis*)	Topically applied for irritated papillomatous lesions with sterile lubrication jelly with enough volume to contact the papilloma surface[15]	Most bird species
Yarrow (*Achillea millefolium*)	Topically used for slow-healing wounds and skin inflammation as well as clotting in oozing wounds[15]	Most bird species
Eye Sea	Screech owls: average weight: 208 g (0.2 kg [0.44 lb]) Dilute 1 capsule into 10 mL of water, then make into 0.5-mL aliquots for 20 animals Dose: give one-twentieth of a capsule per 0.2–1.36 kg[16]	Screech owls, unpublished data

(*continued on next page*)

Box 1
(*continued*)

Agent	Dosage	Species
OcuGlo (small bottle)	1 capsule orally for animals less than 4.5 kg (10 lb)[17]	Chinese goose
Imuno-2865	1000 mg SID for estimated weight (3 kg)[18]	Penguins
Shana-Vet	500 mg SID for estimated weight (3 kg)[18]	Penguins

Abbreviations: ALA, alpha lipoic acid; IM, intramuscular; PO, orally; prn, as needed; q, every; SC, subcutaneously; SID, single intradermal dose; tsp, teaspoon.

companies that hold these seals of approval proactively provide the best quality supplements to their consumers, and veterinarians should responsibly seek out these products. A recent study found that 34 of 44 herbal products tested were contaminated with some type of substitution or filler, which poses serious health risks to consumers.[28] This study shows the importance of finding a company that is certified at executing good manufacturing practices (GMPs) for pharmaceutical grade and not food-grade standards. GMP refers to the regulations promulgated by the FDA under the authority of the Federal Food, Drug, and Cosmetic Act. Failure of GMP-certified firms to comply with GMP regulations can result in serious consequences including recall fines and incarceration. GMP regulations address issues including record keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling.[27] Manufacturers that do not comply with GMP standards should not be recommended.

Box 2
Ferrets, rabbits, guinea pigs, and rodent nutritional supplements and dosages

Agent	Dosage	Species
Ferrets		
Nutri-Cal (EVSCO)	1–3 mL/animal PO q 6–8 h[13]	Ferrets
Saw palmetto	0.15 mL/animal PO q 12 h[13]	Ferrets
Yeast, brewer's	1/8–1/4 tsp PO q 12 h[13]	Ferrets
Rabbits		
Lactobacilli	Administer PO during antibiotic treatment period, then 5–7 d beyond cessation[13]	Rabbits
Silymarin	4–15 mg/kg PO q 8–12 h[13]	Rabbits
(milk thistle)	20–50 mg/kg PO q 24 h[13]	Rabbits
Hedgehogs		
Lactobacilli	2.5 mL/kg q 24 h[13]	Hedgehogs
Rodents		
Vitamin C (ascorbic acid)	50–100 mg/kg PO, SC, IM q 24 h[13]	Guinea pigs
Lactobacilli	PO during antibiotic treatment period, then 5–7 d beyond cessation; give 2 h before or 2 h following antibiotic treatment[13]	All rodent species
Echinacea	2 mg/mouse/d[15]	Mice
Milk thistle (*Silybum marianum*)	4–15 mg/kg PO q 8–12 h[13]	Most rodent species

Box 3
Reptiles, fish, cetaceans, and primate nutritional supplements and dosages

Reptiles		
Iron dextran	12 mg/kg IM 1–2 × wk × 45 d[13]	Crocodilians/iron deficiency; in other species for anemia[96]
Vitamin A	1000–5000 U/kg IM q 7–10 d × 4 treatments[13]	Most reptile species
	2000 U/kg PO, SC, IM q 7–14 d × 2–4 treatments[13]	Most reptile species
Vitamins A, D_3, E (Vital E+A+D, Stuart Products)	0.15 mL/kg IM, repeat in 21 d[13]	Most reptile species
	0.3 mL/kg PO, then 0.06 mL/kg q 7 d × 3–4 treatments[13]	Box turtles
Vitamin B complex	0.3 mL/kg SC, IM q 24 h[13]	Most reptile species
	25 mg thiamine/kg PO q 24 h × 3–7 d[13]	Most reptile species
Vitamin B_1 (thiamin)	50–100 mg/kg PO, SC, IM q 24 h[13]	Piscivores
	30 g/kg feed fish PO[13]	Crocodilians
Vitamin B_{12} (cyanocobalamin)	0.05 mg/kg SC, IM q 24 h[13]	Snakes, lizards
Vitamin C	10–20 mg/kg SC, IM[13]	All reptile species
Vitamin D_3	1000 IU/kg IM, repeat in 1 wk[13]	Most reptile species
Vitamin E/selenium (L-Se, Schering)	1 IU vitamin E/kg IM[13]	Piscivores
	50 IU vitamin E/kg + 0.025 mg selenium/kg IM[13]	Lizards
Vitamin K_1	0.25–0.5 mg/kg IM[13]	Most reptile species
Carnitine	250 mg/kg[19]	All reptile species
Methionine	40–50 mg/kg[19]	Dose seems safe in most reptiles
Milk thistle (*Silybum marianum*)	4–15 mg/kg PO q 8–12 h[13]	Lizards
Omega-3	600 mg SID at 27 kg[20]	Atlantic Ridley sea turtle
Lecithin	1200 mg SID at 27 kg[20]	Atlantic Ridley sea turtle
Alpha lipoic acid	100 mg SID at 27 kg[20]	Atlantic Ridley sea turtle
Artichoke and milk thistle	1650 mg SID at 27 kg[20]	Atlantic Ridley sea turtle
Fish		
Iodine derivative	10–30 mg kg body weight-1 week-1[21]	Elasmobranchs: this dosage is recommended in facilities where goiter is expected to develop. This dosage is more than a dietary supplement and may be high for some species
Cetaceans		
Imuno-2865	5–15 mg/kg[22,23]	Atlantic bottlenose dolphin
Serenin Vet	Follow Animal Necessity dosing guidelines by weight[24]	Atlantic bottlenose dolphin
Shana Vet	Follow Animal Necessity dosing guidelines by weight. Topical form should be applied after drying the area as the cream is water resistant[24]	Atlantic bottlenose dolphin
Alpha lipoic acid	2–3 mg/kg[25]	California sea lion
Primates		
Tryptophan	Tryptophan supplementation at 100 mg/kg q 24 h in the afternoon reduced self-mutilation[26]	Rhesus monkey

Box 4
Veterinary supplement resources

- National Center for Complementary and Alternative Medicine (NCCAM): http://nccam.nih.gov/
- American Holistic Veterinary Medical Association (AHVMA): http://www.ahvma.org/
- Veterinary Botanical Medical Association (VBMA): http://www.vbma.org/
- Natural Standard: http://www.naturalstandard.com/
- National Animal Supplement Council (NASC): http://www.nasc.cc/
- Animal Necessity, LLC: http://animal-necessity.com
- Oxbow Animal Health: http://www.oxbowanimalhealth.com/
- Harrison's Bird Foods: http://www.harrisonsbirdfoods.com/products/avix.html
- Lafeber: http://lafeber.com

VITAMIN AND MINERALS

Vitamin A

Vitamin A is composed of the fat-soluble retinoids, including retinol, retinal, retinoic acid, and retinyl esters.[29] Preformed vitamin A (retinol and its esterified form, retinyl ester) and provitamin A carotenoids (beta carotene, alpha carotene, and beta cryptoxanthin) are two forms commonly found in food.[29] Both of these forms of vitamin A are converted into retinol, then oxidized first to retinal, and then to retinoic acid.[29] Vitamin A is stored in the liver as retinyl esters. Retail supplements on the market that contain vitamin A are usually found in forms of animal-based retinol esters (palmitate, acetate) or plant-based precursors (beta carotene). Careful attention is advised as to which type of vitamin A is administered to exotic patients. The smaller the animal, the less room for error, and the greater the chance of toxicity because this is a fat-soluble vitamin that, in excess, is stored in adipocytes.[30] Retinyl palmitate is a more stable version of retinol, but skin must further break down retinyl palmitate, therefore much higher concentrations are required to provide the similar benefit.[31,32] Two molecules of vitamin A are formed from 1 molecule of beta carotene. The body converts beta carotene into retinol in the amount needed, which makes this a safer form of vitamin A.[31,32]

Herbivores, such as green sea turtles, feed on seagrass and convert beta carotene to vitamin A.[33] Carnivores and many turtles, such as the box turtle, are less capable of converting beta carotene to vitamin A.[33] These animals require an animal-based retinol ester in their diets.[33] In order to provide adequate vitamin A, a high-quality diet should be provided, including dark leafy greens and orange and yellow vegetables. Birds on an all-seed diet should be changed to a commercial high-quality pelleted feed that is always well within its expiration date. Insectivores should ingest insects that are fed, or gut-loaded with, vegetables. In addition, the insects should be dusted weekly with a multivitamin containing preformed vitamin A.[33]

Vitamin C

Deficiencies in vitamin C and zinc may result in abnormal cartilage development and maintenance.[34] Sandtiger sharks (*Carcharias taurus*) in captivity have been reported to have spinal deformities related to a nutritional deficiency of vitamin C, vitamin E, and zinc.[34] In exotic pets, hypovitaminosis C (scurvy) is commonly seen in the guinea pig. Owners should feed commercial guinea pig pellets containing fortified levels of vitamin C that exceed maintenance requirements. Approximately one-half of vitamin C is oxidized and inactivated within 90 days in fortified diets. Dampness, heat, and light can reduce the level of vitamin C, so pet owners should be aware of expiration dates both on diets and supplement bottles. Some clinical signs include poor fur coat quality, swollen knee joints, lameness, gingival bleeding, chronic nonhealing skin wounds, and diarrhea.[33] Maintenance vitamin C requirements for guinea pigs are 10 mg/kg body weight daily, 30 mg/kg body weight for pregnant animals, and higher doses (50 mg/kg) may be suggested for sick or convalescent animals.[33] Hypervitaminosis C has been reported in guinea pigs, so careful and accurate dosing when supplementing should be monitored.[35] Vitamin C also increases absorption of iron so caution must be exercised in animals prone to hemachromatosis or if there is iron supplementation.

Vitamin D, Calcium, and Phosphorus

Unlike other mammals, rabbits absorb calcium readily from the GIT without vitamin D or activation of calcium-binding proteins within the GIT. Owners must not oversupplement rabbits with vitamin D because hypercalcemia can occur. Many modern species, including amphibians, reptiles, birds, and most mammals, still depend on sunlight for their vitamin D requirements.[36,37] Avian skin covered with plumage cannot synthesize vitamin D. Nonfeathered skin, including the legs, has a 10-fold higher concentration of 7-dehydrocholesterol.[36,37] Cats have no 7-dehyrocholesterol in their skins and therefore cannot synthesize vitamin D_3. They depend solely on diet for their vitamin D_3 requirement.[35,36]

Commercial supplements are available with and without vitamin D_3. A supplement that contains vitamin D_3 and not vitamin D_2 is recommended. Vitamin D_2 has not been shown to support normal skeletal mineralization in amphibians.[35,36] The author recommends that if an exotic pet is exposed to natural sunlight or full-spectrum lighting (ultraviolet B range, 285–320 nm), then caution should be taken to avoid oversupplementation with vitamin D_3.[38] Vitamin D_3 is fat soluble, which can induce toxicity, and, in excess, is stored in adipocytes.

Supplemental calcium can be provided by dusting food with pure calcium carbonate, calcium citrate, or calcium lactate. Calcium gluconate is also acceptable and can be compounded as a liquid for oral administration. Pure calcium that is free of heavy metals, such as lead, should be used to make sure there is no interference with normal metabolism. Calcium sources include oyster shell, cuttle bone, ground calcium carbonate tablets, and gut loading insects with calcium. Pelleted diets are important for psittacines to avoid deleterious self-selection of calcium-deficient seeds.

Deficiency of vitamin D has been linked to immunosuppression and autoimmune disease.[39] Vitamin D receptors are present in tissues involved in calcium homeostasis and also in tissues associated with immunomodulation.[39] In addition, vitamin D possesses antiinflammatory properties such as augmenting macrophage function and the inhibition of inflammatory cytokines such as tumor necrosis factor alpha and interleukins.[39] The author (JMF) found that vitamin D levels in wild-caught, whole frozen capelin, smelt, and squid were negligible (JMF, unpublished data, 2014). Therefore, when feeding carnivorous aquatic species housed indoors, it is prudent to supplement with Vitamin D.

Thiamine and Vitamin E

Thiaminase in the meat of certain fish species is not destroyed by the freezing process and, over time, especially in poorly stored fish, continues to break down thiamine.[40–43] If animals are not supplemented with thiamine, neurotoxicity can occur, and manifests as ataxia, muscle tremors, blindness, and even death.[40–43]

Vitamin E deficiency causes anorexia and painful swollen subcutaneous nodules. Steatitis has been reported in reptiles such as crocodiles and sea turtles, as well as in birds, mammals, and fish.[44] Marine and cold-water fish store energy as polyunsaturated fats, which in the presence of oxygen induce peroxidation and rancidity, which in turn depletes vitamin E levels.[45] Fish-eating animals should be fed wholesome, fresh fish that are fresh frozen and thawed in cool temperatures.[44]

Vitamin E is an important antioxidant that protects unsaturated lipids from degradation by reactive oxygen species.[46] The quantity of unsaturated fatty acids in tissues dictates the vitamin E requirement.[46] The author (JMF) found that vitamin E levels in wild-caught, whole frozen Atlantic herring, capelin, and smelt were negligible.[47] Aquatic mammal, avian, fish, and reptile species on carnivorous diets need vitamin E supplementation because of the high proportion of dietary unsaturated fatty acids. Excessive concentrations of vitamin E may inhibit vitamin C absorption.[34] Vitamin E should be provided in combination with another antioxidant such as vitamin C or grape-seed extract (GSE), which reduce tocopheroxyl radicals back to their active state.[48,49] In addition, GSE is a more potent free radical scavenger than vitamins C and E.[50]

Iodine

Iodine deficiency can be caused by lack of dietary intake, iodine-deficient soils, and dietary goitrogens. Goiter has been reported in giant terrestrial tortoises (*Geochelone elephantopus* and *Testudo gigantea*) as well as budgerigars when fed goitrogenic vegetables.[51,52] Vegetables high in goitrogens should be fed only intermittently; these include kale, bok choy, turnips, cabbage, broccoli, and cauliflower.

Iodine is also essential for fish and dietary requirements are still unknown. Diffusion uptake of iodide occurs across the gills and stomach, with excretion primarily in the kidneys and rectal gland.[21] A disinfectant, such as ozone, causes a reduction of iodide.[53] Normal iodine uptake can also be inhibited by increased levels of bromide, fluoride, calcium, cobalt, manganese, and sulfides.[21]

Herring, capelin, and smelt are fish that are commonly fed to aquatic species. In 1989, Lall[54] reported that substantial losses of iodine occur during processing of fish meal. Levels of iodine measured in 3 types of fishmeal were low (ie, 5–10 mg per kg).[54] The author (JMF) found that iodine, selenium, and vitamin C levels in these fish, when frozen, are negligible.[47] Vitamin C deficiency can also reduce iodide uptake.[21] Selenium deficiency has been associated with a form of hypothyroidism.[44] Although this type of Se-deficiency hypothyroidism has only been described in mammals, it should also be suspected in reptiles fed foods from selenium-deficient regions as well as aquatic species fed frozen-fish diets.[44]

Because safe levels of iodine have not been reported for many exotic species, caution should be exercised with iodine supplementation. Nutritional requirements for iodine depend on age, growth, sex, physiologic status, environmental stress, disease, reproductive stage, lactation, and iodine content in the water.[54] To meet daily requirements, humans must trap 60 μg of dietary iodine; daily recommendations for growth are 50 to 150 μg; for reproduction 175 to 200 μg; and lactation 290 μg.[44] Because reptiles have a lower metabolic rate than humans, an adequate daily level is approximately one-fourth to one-third of human levels (0.3 g/kg body weight).[44] Iodine can be supplemented as iodized salt (potassium iodide, sodium iodide, or calcium iodate) or algae (seaweeds) in powder and tablet forms.[21] There are several macroalgae, such as *Spirulina* and *Chlorella vulgaris*, in which it has been determined that iodine content depends on the method of algae cultivation.[55,56] Other algae such as dried kelp contain an average iodine content of 0.062% to 620 μg/g, which is about 8 times the iodine content of iodized salt.[44] The kelp industry is well regulated in Norway and Japan, but not all kelp products sold in the United States are regulated.[44] Because iodine content of algae can vary, the authors recommend contacting the company from which algae is purchased to determine the concentration and source of iodine.

SUPPLEMENTAL SUPPORT

Specific Antioxidants with Beneficial Ocular Effects

Carotenoids include lutein, zeaxanthin, and lycopene. Lutein and zeaxanthin are oxycarotenoids found in dark leafy vegetables, egg yolks, and colored fruits. They selectively accumulate in the lens and the retina; they are also found in the uveal tract with trace amounts found in the cornea and sclera.[57,58] Lutein and zeaxanthin may be particularly effective in the prevention or slowing of cataract; increased plasma and/or dietary levels of these carotenoids are associated with decreased risk of cataract formation. Animals fed diets lacking lutein and zeaxanthin were more susceptible to cataract development. Lutein and zeaxanthin also have protective effects on the retina against blue light and oxidative stress.[59] Together with the metabolite mesozeaxanthin, they accumulate in photoreceptor axons and interneurons of the inner plexiform layer.[60] Lutein exists primarily in the rod photoreceptor outer segments.[61] In birds, lutein and zeaxanthin accumulate in the retina, specifically in the cone-rich retina, where they exist as esters in oil droplets.[62] Dietary lutein was detectable in the blood and retinas of supplemented marine mammals and green sea turtles.[63,64] Lutein also has antiinflammatory effects via the nuclear factor kappa B pathway.[65] Lycopene is found primarily in tomatoes and has the highest physical quenching rate constant with singlet oxygen species compared with all other known carotenoids. Lycopene has been shown to protect against cataract formation in vitro and in animal models.[66]

Flavonoids are also phytochemicals with antioxidant and antiinflammatory properties. Flavonoids are found in bilberry, GSE, green tea extract, and quercetin. Bilberry and GSE inhibit oxidative stress and GSE has been shown to inhibit formation of certain types of cataracts in animal models by increasing glutathione, the predominant antioxidant system in the lens.[67] Epigallocatechin gallate (EGCG), the principal flavonoid in green tea, may be a beneficial complement to glaucoma therapy because it protects against ischemia/reperfusion injury[68] and seems to have neuroprotective effects on the inner retina.[69,70] EGCG also protects photoreceptors in models of oxidative stress–induced retinal degeneration.[71] Green tea catechins have been detected in the retina and aqueous humor after oral administration. Similar to other plant extracts, green tea has many constituents and all have some effective antioxidant capabilities; therefore their combination provides free radical scavenging effects, antioxidant effects, and lipid peroxidation inhibition.[72] Green tea extracts likely convey protective effects against cataract formation, as has been shown in an animal model of selenite-induced cataracts.[73] Quercetin reaches measurable plasma levels when provided in meals rich in various fruits and vegetables.[74] Following uptake into the lens, quercetin is metabolized to 3′-O-methyl quercetin, which is also protective against oxidative stress.[75] Therefore, quercetin may have protective effects against cataract formation.

Omega fatty acids (OFA) of the n-3 and n-6 series are important components of cell membrane phospholipids and cannot be interconverted.[76] Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), commonly termed omega-3 fatty acids, are found in fish and other marine animals because they are synthesized at the base of the aquatic food chain by phytoplankton. Omega-3 fatty acids are also found in flaxseed, pumpkin seeds, and green leafy vegetables. Preformed dietary polyunsaturated fatty acids, such as fish oils, are a more efficient way to supplement diets with DHA than flaxseed oil. DHA is present in high levels in the retina, cerebral cortex, sperm, and testis,[77] and is found in the photoreceptor outer segments. Together with lutein and zeaxanthin, DHA promotes photoreceptor health and protection against oxidative stress.[78]

Alpha lipoic acid (ALA) is a cofactor for alpha-keto-dehydrogenase complexes, participating in acyl transfer reactions.[79] ALA and its reduced form, dihydrolipoic acid, have potent antioxidant abilities.[80] ALA is normally found in small amounts in mammalian tissues bound to enzyme complexes. This bound form is unavailable to function as an antioxidant. However, free exogenous ALA may be an effective thiol substitute.[81] ALA has been shown to protect against cataract formation and showed increases in ascorbate, vitamin E, and glutathione.[82]

By supplementing a variety of antioxidant nutraceuticals, endogenous and exogenous eye diseases may benefit. A mouse model of inherited retinal degeneration had increased antioxidant levels, reduced photoreceptor cell death, and reduced oxidatively damaged DNA when supplemented with lutein, zeaxanthin, ALA, and *Lycium barbarum* extract.[83] A commercially available antioxidant blend was safely used in a Chinese goose with cataracts for more than a year, and the cataracts remained stable.[17] A similar nutraceutical blend has also been used safely in screech owls in a recent toxicity study.[16] It is the authors' opinion that a variety of antioxidants is ideal as a complement to an appropriate diet.

LIVER SUPPORT

Hepatic lipidosis (excessive lipid accumulation in hepatocytes) is a metabolic derangement caused by multiple factors linked to diet, obesity, reduced activity, and seasonal vitellogenesis in reptile, avian, and aquatic species.[19,20,84,85] Methionine, biotin, and choline are essential nutrients for humans and animals and a deficiency may inhibit formation of lipoproteins, thereby inhibiting mobilization of fat and resulting in hepatic lipidosis. This condition is commonly seen in psittaciforme species such as budgerigars, cockatiels, Amazon parrots, and cockatoos.[86] Treatment entails correcting dietary or environmental factors, addressing concurrent disease, and supporting liver regeneration. In birds, the level of protein should be decreased to approximately 8%, vitamin A reduced to 1500 IU/kg of diet, and branched chain amino acids (leucine, isoleucine, and valine) should be increased in a ratio of 2:1 to aromatic amino acids.[87] Ahlstrom and colleagues reported the beneficial use of nutraceuticals for a case of hepatic lipidosis in an Atlantic Ridley sea turtle (*Lepidocheyls kempii*).[20] The supplementation protocol for this animal included artichoke and milk thistle, ALA, lecithin, and omega-3 fatty acids; these resulted in dramatic improvements in serum biochemistry liver values as well as behavior, characterized by normal diving and swimming activity.[20]

ALA

ALA is a naturally occurring dithiol compound that is an essential cofactor for mitochondrial bioenergetics enzymes.[87] ALA recycles glutathione, which is considered the universal antioxidant found in highest concentrations in the brain, eye, heart, and liver.[88,89] Glutathione is a nutrient formed from 3 amino acids, 2 of which are the essential amino acids cysteine and methionine. Glutathione levels can become depleted when there is a heavy toxicity load in the liver, allowing toxins to build up in the body. Glutathione is needed by the liver in order to change fat-soluble toxins into water-soluble toxins, which are then excreted by the kidneys.[88] ALA has been studied in Japanese quail to ameliorate undesired lipid peroxidation effects caused by heat stress as well as preventive effects of atherosclerosis.[12,90] The maximum tolerated dose for cats is 13 mg/kg body weight, which is significantly lower than the single oral dose tolerated in humans, dogs, and rats: 120, 126, and 635 mg/kg, respectively.[89] Further research needs to be performed to assess safe doses for exotic species. ALA also recycles vitamin C (ascorbic acid) and has diverse antioxidant and pharmacologic properties including improving glycemic control, directly terminating free radicals, and chelating transition metal ions including iron and copper.[80] ALA decreases blood glucose levels, therefore animals that are diabetic and being administered insulin or with low blood glucose levels should be monitored carefully.

S-adenosy-L-methionine

S-adenosy-L-methionine (SAMe) also increases glutathione levels using a different mechanism. SAMe donates its methyl group to choline transforming into S-adenosyl-homocysteine (SAH). Homocysteine is normally converted to SAMe, which recycles back to methionine or, alternatively, is converted to cysteine and then to glutathione. Vitamin B_6, B_{12}, and folic acid (SAMe's main cofactors) are essential for the recycling of homocysteine.[91] If these B vitamins are deficient in the diet, SAMe may not break down properly and homocysteine levels may accumulate to unsafe levels.

SAMe plays a role in more than 100 reactions catalyzed by methyltransferases. These reactions include biosynthesis of creatine; formation of neurotransmitters and some neuroreceptors; biosynthesis of phospholipids; biosynthesis of L-carnitine; and reactions involving DNA, RNA, and proteins.[92] Hepatic SAMe serves as the major source of hepatic glutathione and systemic thiol. Increased blood homocysteine levels are a risk factor for atherothrombotic vascular disease and other cardiac diseases.[93]

Lecithin, Inositol, Phosphatidylcholine, and Methionine

Lecithin, inositol, and phosphatidylcholine (PC) are in a class of phospholipids that incorporate choline as a headgroup. Choline is lipotropic, acting on fat metabolism by hastening removal and converting fats into phospholipids, which are more rapidly transferred from the liver into blood.[19] The most likely toxic change of fatty liver disease is damage to the mitochondrial membranes causing inability of the liver parenchymal cells to metabolize fats.[94] PC is important in the known mechanisms of liver homeostasis, toxic liver damage, and the liver's recovery processes.[94] PC is a safer means of dietary choline repletion than choline itself.[94] Methionine is also a precursor to choline with reported lipotropic effects.[19]

Omega-3 Fatty Acids

Omega-3 fatty acids have several beneficial properties and supplementation has been used in various exotic pet species for hepatic lipidosis. One study evaluated 10 European polecats (*Mustela putorius*), the wild form of the domestic ferret, in which food was withheld for 5 days with 10 control animals fed a commercial diet.[95] The food-deprived animals showed microvesicular and macrovesicular hepatic steatosis. The most important biochemical manifestations shared by the polecats and humans with nonalcoholic fatty liver disease (NAFLD) were decreased total n-3 PUFA percentage and an increase in the n-6/n-3 PUFA ratio in liver and white adipose tissue.[95] Various mechanisms have been described through which consumption of fish oil has been beneficial in the alleviation of NAFLD, such as (1) decreased plasma nonesterified fatty acid concentrations; (2) decreased de novo lipogenesis, very-low-density lipoprotein export, and plasma triglyceride concentrations; and (iii) decreased adipocyte size and visceral fat content.[96]

Artichoke, Milk Thistle, and Dandelion

Concomitant intake of plant extracts containing cytoprotective compounds may increase the efficacy of treating liver disease. Artichoke, milk thistle, and dandelion have antioxidant liver protectant properties. Dandelion is a common plant fed to herbivorous reptile species. These supplements have been shown to have few side effects, although artichoke and dandelion do have diuretic properties and should be used with caution in dehydrated patients.

Artichoke (*Cynara scolymus*) is a flower extract that contains cynarin, a compound that promotes production of bile. Artichoke leaves contain caffeoylquinic acids, which help to improve digestion and aid in liver, gallbladder, and diuretic kidney function. This plant is used for medicinal purposes; it not only has hepatoprotective action but also prevents atherosclerosis and hyperlipidemia or dyspeptic disorders.[97]

Milk thistle (*Silybum ebumeum* or *Silybum marianum*) is a waxy-lobed, thorny plant that is a member of the daisy family. Milk thistle contains 80% silymarin, an important compound that nourishes the liver, helps protect it from cellular damage, and upregulates the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase.[98] Hepatoprotective effects against mushroom poisoning have been reported with silybin, the active ingredient of silymarin.[98] Pigeons were infected with aflatoxin after a 21-day period of milk thistle supplementation and results showed that there was a reduction in bile acid levels and white blood cell counts compared with nonsupplemented control animals.[98] Further studies are warranted to evaluate the hepatoprotectant effects of this supplement in avian species. Anecdotal accounts from bird owners report that they observe improved appetites in their animals after being supplemented with milk thistle.

Dandelion (*Taraxacum officinale*) has a wide array of therapeutic functions including choleretic, diuretic, antioxidant, antiinflammatory, and hepatoprotective properties.[99] A few studies have been performed evaluating the hepatoprotectant effects of dandelion in mice. Results in one study showed hepatoprotective effects after acetaminophen hepatotoxicity with a possible mechanism involving its free radical scavenger activities. This effect was attributed to the extract's content of phenolic compounds.[99] Another study used a murine model of methionine-deficient and choline-deficient diet, which induced nonalcoholic steatohepatitis (NASH). Results suggested that dandelion leaf extract has beneficial effects on NASH, mainly because of its antioxidant and antiinflammatory activities.[100]

IMMUNE, ANTIFUNGAL, ANTIVIRAL, ANTIINFLAMMATORY SUPPORT

In recent years, advances in testing of the different facets of exotic species' immune systems have resulted in a increase of knowledge, and research continues to expand this understanding. Pilot studies evaluated immune function using Imuno-2865 (PDS-2865) in cetacean species.[22,23] This new supplement is a beta-glucan that shows encouraging findings in improving human lymphocyte activation and interleukin activity.[101–103] Beta-glucans are polysaccharides with immune-modulating properties and are found in the bran of cereal grains; the cell wall of baker's yeast; and certain types of fungi, mushrooms, algae, and plants including members of the Poaceae (or Gramineae) family.[101–103] Various beta-glucan supplements are commercially available.

Arabinogalactan is found in various plants, with the highest concentrations occurring in larch trees. This starchlike chemical enhances beneficial gut microflora by increasing short-chain fatty acid production (primarily butyrate), which is both essential for proper immune health of the colon and is the preferred substrate for energy generation by colonic epithelial cells.[104] The effectiveness of beta-glucans is enhanced when delivered in small particle sizes (microparticulates) to help promote improved absorption and function in the immune system.[101–103] The laboratory extraction process used to break down or predigest beta-glucan polysaccharide molecules into smaller components, called hemicelluloses, makes them an ideal food supplement to support and enhance immune system function.

Eicosanoids are derived from omega-3 and omega-6 fatty acids. Omega-6 eicosanoids (gamma-linolenic and arachidonic acid [AA]) are proinflammatory, whereas omega-3 fatty acids (EPA and DHA) have antiinflammatory properties and may serve as potential therapeutic agents for cancer prevention and control.[105] In animal models, an increased ratio of dietary n-3 to n-6 fatty acids has been shown to inhibit the development of mammary cancer.[105] Omega-3 fatty acids exert their antiinflammatory effects in skin by acting as natural 5-lipooxygenase inhibitors of AA, as well as having antileukotriene and antineutrophilic properties.[106]

Common fungal organisms often invade the epidermis, keratin layer, and respiratory tract of various exotic species. Aspergillosis is a significant avian disease that can be challenging to diagnose. Prophylactic treatment with itraconazole in penguins is a common practice, in order to reduce morbidity and mortality, especially during periods of transport stress.[18] However, chronic use of itraconazole can promote antifungal drug resistance. A recent pilot study was therefore conducted to investigate whether an alternative prophylaxis using supplements (squalene, calendula, triacontanol, and beta-glucans) would have less adverse effects.[18] During a potentially stressful exhibit modification period, penguins were evaluated before and after supplementation using complete blood count, protein electrophoresis, *Aspergillus* antibody testing, and galactomannan antigen testing. Prophylactic supplementation of Shana-Vet and Imuno-2865 (PDS-2865) was used safely in 25 penguins and none of the birds developed fungal disease.[18]

Squalene is a natural lipid triterpene and is also a vital precursor of cholesterol biosynthesis.[107] Squalene is synthesized in humans, sharks, and other species.[107] Because of its significant dietary benefits, biocompatibility, and other advantageous properties, squalene is extensively used as an emollient and for photoprotection of skin in pharmaceutical formulations, and is used synergistically to enhance the cytocidal effect of antifungals.[107] High intracellular fungal squalene concentrations are thought to interfere with fungal membrane function and cell wall synthesis.[107] *Calendula* is a flower that contains sesquiterpenes, glycosides, saponins, xanthophylls, triol triterpenes, and flavonoids that have antiinflammatory effects.[108] This plant has been found to possess antifungal activity against 22 strains of pathogenic *Candida* species.[108] A major threat to agriculture and to human health is *Aspergillus flavus*, a common filamentous fungus that produces aflatoxins.[109] In the *A flavus* life cycle, the transition from sclerotia to conidia life-forms is governed by both lipoxygenase activity and cell density.[109] When exposed to *Aspergillus fumingatus*, *Candida albicans*, or *Cryptococcus neoformans*, alveolar macrophages may promote peroxidation of surfactant lipids in the lungs.[110] Found in high concentrations in beeswax and plant cuticle waxes, triacontanol is a 30-carbon alcohol that inhibits lipoxygenase.[111] Triacontanol has antiinflammatory effects that may be mediated through inhibition of lipid peroxidation.[111,112] Results of a study using a guinea pig skin model suggest that triacontanol-containing mixtures represent an alternative treatment modality to topical steroid applications.[111]

In addition to its antiinflammatory effects, triacontanol and docosanol show antiherpetic properties.[111,112] Docosanol, also known as behenyl alcohol, is a saturated 22-carbon aliphatic alcohol. Docosanol inhibits fusion between envelope viruses and host cells, thus blocking viral entry and replication.[113]

Aloe vera (L.) Burm. f. is a perennial succulent xerophyte found in various supplements.[114] The medicinal effects of this plant are attributed to polysaccharides found in the parenchyma of the inner leaves.[114] Therapeutic effects include antiinflammatory, laxative, immunostimulating, antibacterial, wound and burn healing, antiulcer of the GIT, antitumor, and antidiabetic activities.[114]

Shana-Vet contains calendula, triacontanol, docosanol, aloe vera, and squalene. Further research using this supplement (both topical and oral forms) is suggested in animals with herpesvirus. Oxbow Natural Science Skin & Coat contains chamomile, canola, and red palm oil, which provide antioxidant and antipruritic properties for skin-related diseases. Harrison's Booster and Sunshine Factor also contains red palm oil which is composed of approximately 50% saturated and 50% unsaturated fatty acids.[115] This antioxidant-rich oil also has significant concentrations of carotenoids and vitamin E (75% in the form of tocotrienol).[115] The oil has cardioprotective and antineoplastic properties.[115,116] Oxbow Natural Science Skin & Coat and Harrison's Booster and Sunshine Factor have been suggested to be used in stressed, sick, and feather-picking birds. The manufacturer suggests not combining both supplements.

STRESS/ADAPTOGENS

A variety of behavioral issues have been described in exotic species under human care.[117] Strategies have included behavioral modification, changes to the animals' habitats, modification of social structures for the animal and cohorts, and the use of medications. Anxiolytics and hormonal treatments remain popular adjunctive therapies despite potential side effects.[117,118] Natural alternative supplements have been used that contain ingredients that increase serotonin levels.[24,119–121] Serotonin inhibits aggressive behavior in various vertebrates, ranging from teleost fish to primates.[122–124]

In reptiles, stress has been associated with increased plasma catecholamines and corticosterone, reduced testosterone, decreased hepatic protein and vitellogenin synthesis, reduced food intake, fewer breeding displays, and other suppressed or detrimental behaviors[44] These markers of stress in reptiles are increased after capture, restraint, handling, excessive cold or heat, chemical or visual exposure to a dominant male, and deprivation of food and water.[44] Several nutrients are depleted during stress in mammals.[44] The use of serotonin, endogenous opiates, and dopamine in the diet may be helpful.[44] In stressed lizards (*Calotes versicolor*), vitamin C has been reported to decrease over time.[44] Trials of the herbs chamomile (*Matricaria recutita*), echinacea (*Echinacea* spp), ginko (*Ginko biloba*), ginseng (*Panax ginseng*), kava kava (*Piper methysticum*), and valerian (*Valeriana officinalis*) have been reported in more than 20 species with no untoward effects.[44]

In avian species, behavioral problems such as feather picking can be analogous to compulsive grooming disorders in other species.[125] Therefore, similar neurochemical mechanisms may exist that could result in comparable responses to pharmacologic agents.[125] Some cases of obsessive-compulsive disorder and trichotillomania (hair pulling) respond to serotonergic medications, providing evidence that serotonin dysfunction is involved in mediating these behaviors.[125] Serotonergic agents, such as clomipramine, were used successfully to improve feather picking for a 3-week and 6-week trial compared with a placebo group.[125]

Eleven marine institutions using a serotonin supplement completed a survey evaluating the beneficial use for behavior modification. Information on 9 sea lions and 12 dolphins was analyzed.[124] Behaviors before supplementation included 43% of animals displaying interspecies aggression, 19% self-injurious rubbing behavior, 14% human-directed aggression, and 29% fear and/or anxiety associated with social incompatibility or environmental factors.[124] Most animals (67%) showed improvement as measured by a decrease in negative behavioral signs, with 24% showing a complete resolution of behavioral problems.[124] Only 9% of animals failed to show any improvement.[124] No behavioral, physical, or biochemical side effects were reported for any of the animals in the survey.[124] Serotonin-containing supplements may be an effective alternative for aberrant behavioral conditions in mammals and other exotic pets under human care. Other aquatic veterinarians have reported successful use of this supplement to decrease natural, wild sexual behavior in dolphins, sea turtles, and fish.

SUMMARY

By complementing traditional medicine with holistic and alternative nutrition and supplements, the overall health and wellness of exotic pets can be enhanced and balanced. Hippocrates had a strong belief in the power of the body's immune system, stating that, "Our natures are the physicians of ourselves."[126] Further research is needed for understanding the strengths and uses of supplements in exotic species. Caution should always be taken when supplementing pregnant or immature animals. Scientific evidence is increasing in the use of supplements as an adjunctive therapy to conventional medicine. Going back to the animals' origin and roots bring clinicians closer to nature and its healing powers.

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