Qi Ye Lian and Oxalic Acid: A Caution for Dogs, Cats, and Humans

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Last month we received communication from a veterinarian about a dog that was receiving one of Mayway’s herbal formulas. The circumstances resulted in an adverse event report. At Mayway, we look into every report of adverse effects and each product complaint as a part of our Quality Assurance. In the process of investigating, we discovered some unknown information about qi ye lian (Caulis et Folium Schefflerae) and Plum Flower® Qi Ye Lian tablets. As a result, we are recommending caution in patients with renal impairment, kidney stones and other conditions.

Adverse Event Case History:
An eight-month old, 56-lb. Labrador Retriever, “Bismarck”, was admitted into an animal hospital in the Washington, DC area for what was expected to be a routine neutering. Prior to the surgery, the dog was noted to have a slightly elevated urea nitrogen blood chemistry test, but this was attributed to his high protein diet rather than an indication of renal impairment. For anesthesia, he was given ketamine and diazepam. Pre-operatively, he also received subcutaneous ketoprofen, a non-steroidal anti-inflammatory drug (NSAID) and penicillin G. After a successful surgery, the dog was checked by physical exam and all systems were deemed normal. Bismarck was sent home at 5pm. As part of his post-operative care, Plum Flower® Qi Ye Lian tablets were prescribed by the veterinary doctor. The doctor’s recommended dose was 2-3 tablets, 2-3 times per day. The dog received two tablets in the evening and two in the morning before the herb was discontinued. During the evening and next morning the animal developed excessive thirst and drank 5+ bowls of water and demanded more. The pet’s owners also reported that Bismarck was urinating inappropriately and unaccustomedly in the house. The urine was dark yellow. There was no vomiting or diarrhea.

The next day, the dog was admitted to an Animal Emergency Critical Care facility in serious condition to rule out kidney failure. A physical exam and an ultrasound did not reveal any obvious cause or abnormality. Urine analysis revealed ++ protein, specific gravity of 1.005 (NV= 1.010-1.020), and hemolyzed red blood cells. Blood tests showed an elevated BUN of 47 mg/dL (normal value “NV” = 7-27); Creatinine = 1.9 mg/dL (NV=0.5-1.8); and a Phosphate = 8.7 mg/dL (NV= 2.5-6.8). Other blood tests were within normal limits. This evidence points to renal failure and/or significant impairment of kidney function. The veterinarians at the animal hospital were not sanguine about Bismarck’s prognosis. They placed the dog on IV fluids and then recommended steroids and immunosuppressive chemotherapy, which the pet owners declined.

Mayway was called to see if there had been any reports of problems with administering Qi Ye Lian with animals, to which we replied that there had not been to our knowledge. In fact, our veterinary consultants had suggested the use of Qi Ye Lian for animals, and many vets had expressed satisfaction with their results from its use. After some investigation and several conversations with
the animal hospital, a report of a serious adverse event was reported to the FDA Center for Veterinary Medicine by the attending veterinarian. The owners of Bismarck insisted on homecare and we are happy to report that the dog recovered with no apparent significant long-term problems.

Our Investigation
At Mayway, our investigation discovered some interesting facts. Our Plum Flowers tablet product, Qi Ye Lian is comprised of a water-based extract of a single herb, qi ye lian 七叶莲, Caulis et Folium Schefflerae arboricolae (aka Brassaia actinophylla). The common names of this herb are Schefflera, Umbrella Tree, Australian Ivy Palm, Octopus Tree, and others. It is a common houseplant.

According to Chen in Chinese Medical Herbology and Pharmacology, qi ye lian is bitter, acrid, warm and enters the Liver channel. The recommended dosage (in humans) is 10 to 15 grams. Chen notes under a section entitled Clinical Studies and Research that qi ye lian has been used in vivo to treat various disorders involving pain, including kidney stones. The chemical composition of qi ye lian is listed as: organic acid, mucic acid, fumaric acid, and butanedioic acid.

In the 1986 edition of Pharmacology and Applications of Chinese Materia Medica by Chang and But, qi ye lian is reported to have a bitter taste and a warm property. The active components listed are organic acids including fumaric acid, succinic acid, malic acid, citric acid, y-hydroxybutyric acid, tartaric acid, and aconitic acid; additionally the herb also contains alkaloids, glycosides (cardiac glycosides and saponins), proteins, amino acids, resin, and phenolic substances. The Materia Medica by Bensky, et al. does not have a monograph on qi ye lian.

Interestingly, neither of these authoritative sources mentions oxalic acid as a chemical constituent of this plant. That was discovered when checking the Animal Poison Control Center at the website of the ASPCA.

Where the following information was discovered regarding Schefflera arboicola:

Toxicity: Toxic to Dogs, Toxic to Cats
Toxic Principles: Calcium oxalate crystals
Clinical Signs: Oral irritation, intense burning and irritation of the mouth, lips, tongue, excessive drooling, vomiting, difficulty in swallowing.

Additional information regarding Schefflera and its toxicity to dogs was found at the website of an affiliate of Pets Are Wonderful Support (PAWS), "Poisonous Plants for Pets". Schefflera contains oxalates that bind with calcium in the blood to form calcium oxalate crystals. Symptoms, in addition to the ones from the ASPCA, especially when larger quantities are involved, can include: severe digestive upset, extreme difficulty in breathing, and rapid shallow gasps. In extreme cases, the symptoms become much more severe and can include any of the above with the addition of convulsions, renal failure, coma and death. It is possible to recover from severe calcium oxalate poisoning, however in most cases permanent liver, and kidney damage may have already occurred.

What is Oxalic Acid?
Oxalic acid (H₂C₂O₄) and oxalate ion (C₂O₄²⁻) are essentially the same molecule, differing by dissociation at various levels of pH. Oxalic acid is an organic acid also known as a dicarboxylic acid. (It could be abbreviated COOHCOOH.) As an acid, it is about 3,000 times stronger than acetic acid, which also contains two carbon molecules and which is the carboxylic acid found in vinegar (usually 4.5% v/v acetic acid in water). At physiological pH, its conjugate base, known as oxalate (C₂O₄²⁻), is the predominant species.

Oxalate is a chelating agent for metal cations especially calcium. Calcium oxalate (CaC₂O₄) forms minute crystals which are then excreted in urine. Calcium oxalate is more likely to precipitate out when magnesium levels are low and calcium and oxalate levels are high. When dietary intake of oxalates occurs, serum calcium levels go down and may result in hypocalcemia. Calcium oxalate also collects when there exists impaired renal function from any number of causes. These calcium oxalate crystals can aggregate to form stones that can obstruct the kidney tubules which can lodge at several locations in the urinary tract. An estimated 80% of kidney stones are formed from calcium oxalate.

However, in most individuals, the kidneys excrete oxalates, which are presumed to have no nutritional value, without difficulty. For normal, healthy persons, the risk is trivial considering the amounts of oxalic acid that are consumed in a normal diet. Urinary pH varies from 4.6-8.0. A slightly acid urinary pH (6.0-7.0) aids in the excretion of calcium oxalate while an alkaline urinary pH (>7.0) can cause precipitation of calcium oxalate. In contrast, an even more acidic urinary pH (<6.0) has been associated with gout and the crystallization of uric acid, which is a catabolic product of DNA and RNA turnover.

Oxalates in Food
Oxalates occur naturally in the food we eat and they are found mostly in plant sources. The oxalates present in plants are synthesized during the incomplete oxidation of carbohydrates. The oxalate content of food can vary considerably between plants of the same species, due to differences in climate, soil quality, state of ripeness, or even which part of the plant is analyzed. Variations also may be caused by the different methods used for measuring oxalate in food. In fact, a survey of authoritative sources yields a remarkable spread of test results. Additionally, various reports use different units of measure which further obscures comparison. Look for mg/gm, mg/100g, mg/serving, and even % w/w. Published values for the same foods can vary from negligible amounts to moderately high. Nonetheless, there is general agreement that certain foods are considered moderately high to high in oxalates.
Among those with high levels include: black pepper, parsley, poppy seed, amaranth, beet greens, rhubarb stems, spinach, beets, and Swiss chard, all of which contain 5.5-8.5 mg/serving (1/2 cup). Okra, sweet potatoes, kale, peanuts, turnip greens, and unsweetened chocolate, all of which contain 0.8-1.5 mg/serving (1/2 cup) are among the moderately high group. The leaves from tea contain among the greatest measured concentrations of oxalic acid relative to other plants. However a cup of tea only contains low to moderate amounts of oxalic acid per serving, because so little is used in making the tea. Those with kidney disorders, gout, rheumatoid arthritis, or certain forms of chronic vulvar pain (vulvodynia) are typically advised to avoid foods high in oxalic acid.

Oxalate from plants typically accounts for about one half of urinary oxalate, the other half comes from endogenous synthesis, either from endogenous human collagen catabolism or from consuming animal collagen. The daily turnover of collagen in humans and of animal collagen is a major source of the amino acid hydroxyproline, which is metabolized to oxalate via glycolate. Most meat contains a significant amount of collagen, for example, lean beef, chicken, fish, and lean lamb contain from 2.5%-4.9% collagen by weight. “Composite” meats such as hot dogs, wiener’s, and sausage can contain up to 19% collagen. Gelatin is practically all collagen. Overall, collagen turnover may account for 15%-20% of urinary oxalate daily and animal sources providing another 20-25%. Stone-formers should be advised of the possible risk of consuming gelatin found in gelatin salads and desserts, supplements containing collagen hydrolysates or gelatin, and to avoid composite meats such as wiener’s and sausages.

Actual toxicity, that is to say poisoning, from ingested or endogenous oxalic acid is highly unlikely. The only “food” that contains oxalic acid at concentrations high enough to actually constitute a toxicity risk is the leaves of the rhubarb plant. Rhubarb leaves contain several orders of magnitude more oxalate than other foods. A 1/4 cup (113.5 g) “serving” could contain as much as 1.4% w/w oxalate or 1540 mg/serving. Still, the LD50 in rats for oxalic acid is reported to be 375 mg/kg. Transposing that to dogs, for 1540 mg/serving (1/2 cup). Okra, sweet potatoes, kale, peanuts, turnip greens, and unsweetened chocolate, all of which contain 0.8-1.5 mg/serving (1/2 cup) are among the moderately high group. The leaves from tea contain among the greatest measured concentrations of oxalic acid relative to other plants. However a cup of tea only contains low to moderate amounts of oxalic acid per serving, because so little is used in making the tea. Those with kidney disorders, gout, rheumatoid arthritis, or certain forms of chronic vulvar pain (vulvodynia) are typically advised to avoid foods high in oxalic acid.

The serving size does make a difference however. The bulk herb serving is 10-15 g/day (in a decoction). That translates to 26-39 mg/day, which makes qi ye lian a very high oxalate food. The serving size for tablets is 2-3 tablets, 2-3 times per day. Each tablet weighs 0.3g, so at the maximum dosage of 9 tablets per day this would yield 5.9mg/day which still makes Plum Flower® Qi Ye Lian tablets a high oxalate food. Bismarck, the dog in the case study received 4 tablets over about 12 hours or 2.6mg of oxalic acid. Given the likelihood of a pre-existing renal impairment in this animal, it may be that qi ye lian played a role in his renal failure post operatively, although the relatively small dose, sudden onset, and severe reaction indicate that pre-existing conditions or the surgery probably played a greater role.

Conclusions
Chen in Chinese Medical Herbology and Pharmacology already suggests that qi ye lian should be used with caution in pregnancy. After our research subsequent to this adverse event, Mayway believes that qi ye lian (Caulis et Foliolum Schefflerae) and Plum Flower® Qi Ye Lian tablets should also bear a caution in patients (dog, cat, and human) with renal impairment and/or a history of kidney stones, gout, rheumatoid arthritis, or vulvodynia. Additionally, a study cited in Chen suggests that qi ye lian is appropriate for pain associated with kidney stones, this seems questionable and we think more research needs to be conducted regarding this herb.

References
“Plants Poisonous to Pets”, http://www.pawsdogdaycare.com/Start-Up-Services/Plants-Poisonous-To-Pets-Schefflera.htm

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