Consequences of intratumoral injection of a herbal preparation containing bloodroot (*Sanguinaria canadensis*) extract in two dogs

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Case Description—2 dogs were referred for surgical removal of cutaneous tumors that had previously been treated by intratumoral injection of a herbal preparation containing bloodroot (*Sanguinaria canadensis*) extract.

Clinical Findings—11 days following injection of bloodroot extract into a small dermal tumor, dog 1 developed a large, soft, fluctuant cutaneous mass at the site of injection. Ultrasonographic evaluation of the mass revealed a fluid-filled central cavity with increased echogenicity of the surrounding subcutaneous tissues. Dog 2 had a small dermal tumor under the left mandible that had been treated in similar fashion. However, an exuberant reaction was not observed following injection of bloodroot extract in this dog.

Treatment and Outcome—Both dogs underwent surgical excision of the cutaneous tumors. Histologic evaluation revealed severe necrosis and inflammation in the excised tissues from dog 1. This dog experienced postsurgical wound complications and had a prolonged postsurgical recovery. Similar, although less severe, histopathologic findings were apparent in the excised tissues from dog 2; this dog recovered without complications.

Clinical Relevance—Various products containing bloodroot are marketed on the Internet for topical and parenteral treatment of cutaneous neoplasms in domestic animals. However, the antineoplastic properties, therapeutic efficacy, and adverse effects of these products are poorly described in the veterinary literature. Clinicians should be aware of the potential for harm caused by the use of these products. (*J Am Vet Med Assoc* 2011;239:374–379)

A 2-year-old sexually intact female Golden Retriever (dog 1) was brought to the PUVTH for evaluation of a cutaneous tumor in the right dorsal lumbar area that had been detected by the owner approximately 4 weeks earlier. The tumor measured 2 × 2 × 1 cm, was firm, and was confined to the dermis. Results of cytologic examination of an FNA of the tumor suggested that it was a benign follicular tumor. The owner was advised to monitor the tumor, and surgical removal was offered should the tumor change in size or character.

Three months later, the dog was brought to the referring veterinarian to have the tumor reevaluated. According to the owner, the appearance of the tumor had not changed substantially, but examination of a follow-up FNA was requested for the owner's peace of mind. Results of cytologic examination of an FNA were again suggestive of a benign follicular tumor. At the time that the FNA was performed, the referring veterinarian injected the tumor with 0.2 mL of a herbal preparation[a] containing bloodroot (*Sanguinaria canadensis*) extract. At the time of this injection, the dog was also receiving dietary supplements containing glucosamine–chondroitin sulfate,[b] methylsulfonylmethane,[c] and salmon oil.[d] Six days after injection of the bloodroot extract, the owner noticed that the tumor had become markedly larger and that the skin over the tumor had assumed a reddish-purplish discoloration. The tumor was soft and not warm to the touch, and palpation did not elicit signs of pain. The owner informed the referring veterinarian of the change in tumor size and was instructed to administer a homeopathic product[e] orally to reduce tumoral swelling. The swelling did not resolve, and the dog was returned to the referring veterinarian 9 days after the bloodroot extract injection. At this time, approximately 20 mL of fluid with a serosanguineous appearance was aspirated from the tumor, and the tumor was covered with a bandage. Two days later, the swelling had still not resolved, and the dog was brought to the PUVTH for further evaluation.

On initial examination at the PUVTH, the dog was bright and alert and in generally good condition. A 6 × 6 × 6-cm, soft, fluctuant subcutaneous mass was present in the right dorsal lumbar area, consistent with the location of the previously identified follicular tumor and the site of bloodroot extract injection. The deep extent of the mass could not be ascertained by means of physical examination, but

Abbreviations

FNA	Fine-needle aspirate
PUVTH	Purdue University Veterinary Teaching Hospital

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the mass was not palpably adherent to the underlying subcutaneous tissues. The skin over the mass was not substantially discolored, the mass was not warm to the touch, and palpation of the mass did not elicit signs of pain. A minimal amount of serosanguineous fluid was leaking from a small puncture wound in the mass, presumed to be the site of previous aspiration.

A CBC and serum biochemistry profile did not reveal any clinically important abnormalities. Analysis of a voided urine sample revealed 5 to 9 WBCs/hpf and 1+ bacteria. These were presumed to be contaminants from the lower urinary tract, in that microbial culture of a urine sample obtained by means of cystocentesis did not yield bacterial growth. Ultrasonographic examination of the mass showed that it was encapsulated with an anechoic central cavity containing mobile echogenic material (**Figure 1**). The surrounding fat and subcutaneous tissues showed increased echogenicity suggestive of steatitis or panniculitis.

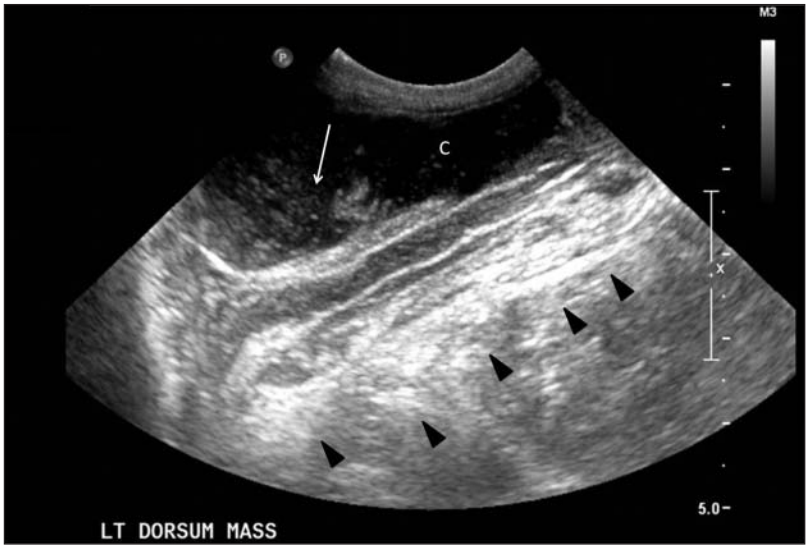

Figure 1—Longitudinal ultrasonographic image of a subcutaneous mass induced by injection of bloodroot extract in a dog (dog 1). The mass contained a central cavity (C) filled with anechoic fluid and flocculent echogenic debris (arrow). The subcutaneous tissues (arrowheads) deep to the mass are intensely echogenic, suggestive of inflammation. Marks on the right side of the image represent distance in increments of 0.5 cm.

The following day, the mass was surgically removed with a 2-cm margin of surrounding grossly normal tissue. On gross inspection, the mass appeared encapsulated and contained serosanguineous to purulent-appearing fluid. The subcutaneous tissues surrounding the mass were discolored dark red to purple. The surgical wound was closed routinely, and a 7.0-mm Jackson-Pratt drain was placed postoperatively. Postoperative analgesia was provided with hydromorphone (0.05 mg/kg [0.023 mg/lb], IV, q 4 h).

The excised mass was submitted in toto for histologic examination. Histologically, the mass was characterized by focally extensive necrosis of the panniculus (**Figure 2**) surrounded by a broad zone of neovascularization and fibroplasia (granulation tissue). There was no evidence of neoplasia in the tissues examined. The morphological diagnosis was necrotizing panniculitis. Excision of the necrotic tissue appeared complete; however, there was evidence of mild panniculitis at the surgical margins.

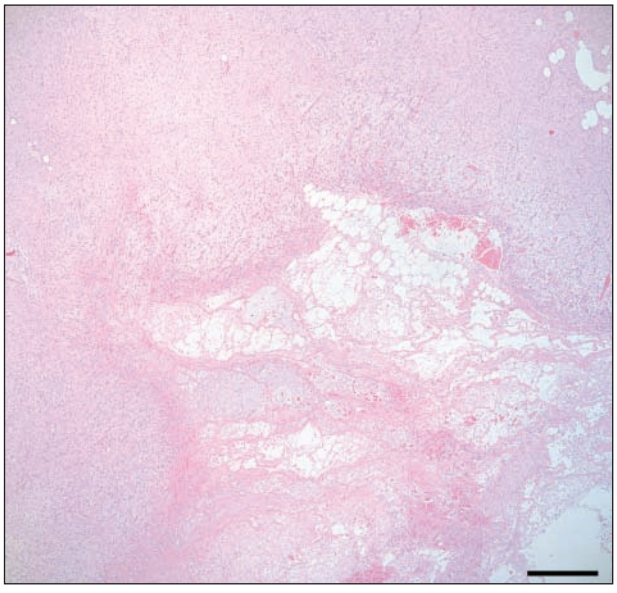

Figure 2—Photomicrograph of the margin of the cavitated subcutaneous mass removed from the dog in Figure 1, twelve days after injection of bloodroot extract. The mass is characterized by central liquefaction and fat necrosis (lower right corner) surrounded by a broad zone of granulation tissue. H&E stain; bar = 500 µm.

The dog recovered routinely from anesthesia, and no immediate postoperative complications occurred. The drain was removed 48 hours after surgery, and the dog was discharged to the owner's care 24 hours after drain removal. Treatment at the time of hospital discharge consisted of cephalexin (25 mg/kg [11.4 mg/lb], PO, q 12 h), carprofen (4 mg/kg [1.8 mg/lb], PO, q 24 h), and tramadol (4 mg/kg, PO, q 8 to 12 h, as needed).

Two weeks later, the dog was returned for a recheck examination. There was mild seroma formation at the ventral aspect of the skin incision, but the dog appeared to be otherwise recovering well. Exercise restriction with strict crate confinement was recommended along with topical application of warm compresses to reduce the seroma formation. Crate confinement and warm compresses did not resolve the seroma, and the dog was returned 1 week later because of enlargement of the seroma. The next day, the dog was anesthetized and a small stab incision was made in the dorsal aspect of the seroma. A suction tip was introduced through the incision, and 200 mL of serosanguineous fluid was removed. Two suction drains were then placed to provide continuous drainage of the seroma. Results of clinicopathologic evaluation of the fluid were consistent with a modified transudate. The dog recovered uneventfully from anesthesia, and an Elizabethan collar was placed postoperatively. Cephalexin (25 mg/kg, PO, q 12 h) was prescribed for antimicrobial prophylaxis. A total of 100 mL of serosanguineous fluid was removed through the drains

over the next 24 hours, and fluid accumulation at the surgical site decreased gradually after this time.

Three days after surgery, the dog chewed through one of the drains while hospitalized overnight. The following day, cytologic evaluation of fluid collected from the drain revealed mild neutrophilic inflammation with intracellular bacteria. Bacterial culture of the drain yielded a *Bacillus* sp that was resistant to most cephalosporins but susceptible to enrofloxacin. Antimicrobial treatment was therefore switched from cephalexin to enrofloxacin (10 mg/kg [4.5 mg/lb], PO, q 24 h). The dog continued to improve, and the second drain was removed 9 days after surgery. The dog was discharged to its owner 3 days later.

The dog continued to heal gradually following discharge from the PUVTH, although other long-term postsurgical complications occurred. Specifically, substantial wound contracture and fibrosis along the surgical scar limited the dog's ability to use its right hind limb. To manage these complications, the dog was treated weekly by a certified canine rehabilitation therapist for approximately 2 months. Physical rehabilitation therapy restored the dog to full mobility, and the dog was in good physical condition at the time of this report.

A 5-year-old sexually intact male Golden Retriever (dog 2) belonging to the same owner as dog 1 was brought to the PUVTH for evaluation of a dermal tumor ventral to the left mandible. The owner had first noted this tumor approximately 2 weeks earlier. Eleven days prior to evaluation at the PUVTH, the tumor had been examined by the referring veterinarian contemporaneously with the tumor in dog 1. Results of cytologic examination of an FNA from the tumor in dog 2 were nondiagnostic but suggestive of benign fibroplasia or a well-differentiated soft tissue sarcoma. At the time the FNA was obtained, the referring veterinarian injected the tumor with 0.1 mL of the same product[a] used in dog 1. At the time of injection, dog 2 was also receiving levothyroxine (0.02 mg/kg [0.009 mg/lb], PO, q 12 h) and dietary supplements containing glucosamine–chondroitin sulfate,[b] methylsulfonylmethane,[c] and salmon oil.[d] According to the owner, mild peritumoral swelling occurred following the injection and lasted approximately 4 to 6 hours. The owner also noted an oily substance leaking from the tumor shortly after injection. Touching this oily substance to her skin elicited an uncomfortable burning sensation, and she immediately rinsed the substance off of her skin and the dog's skin.

Dog 2 was brought to the PUVTH for evaluation of the mandibular mass at the same time dog 1 was initially evaluated. On physical examination, the dog appeared to be in generally good condition. A 1.5 × 1.5 × 1-cm, firm dermal tumor was present ventral to the left mandible. The surface of the tumor was ulcerated with superficial crusting. The owner reported that the crusting and ulceration had been present prior to injection of the bloodroot extract. Further questioning revealed that the dog had been rubbing its chin on objects around the house, and the ulceration was presumed to be related to self-trauma. A CBC, serum biochemistry profile, and analysis of a voided urine sample did not reveal any clinically relevant abnormalities.

The following day, the tumor was excised with a 1-cm margin of surrounding grossly normal tissue. Grossly, the tumor was dark brown and firm, with ulceration and crusting on the epithelial surface. The surgical incision was closed routinely, and the dog was allowed to recover from anesthesia. Postoperative analgesia was provided with buprenorphine (0.015 mg/kg [0.0068 mg/lb], SC).

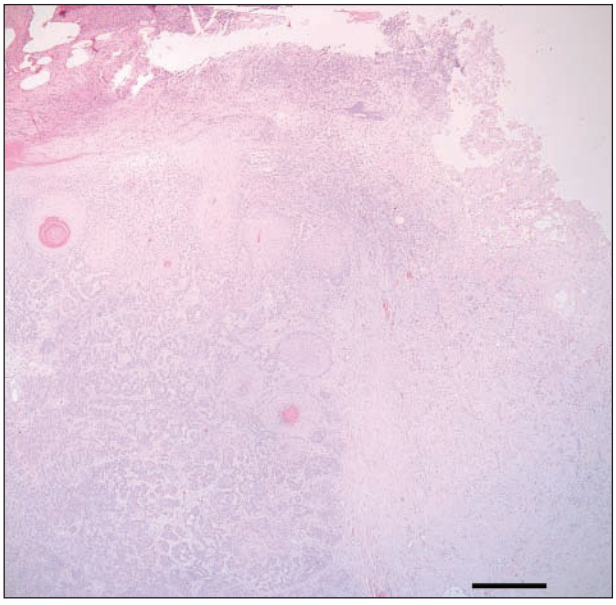

Figure 3—Photomicrograph of a dermal trichoblastoma excised from a dog (dog 2), 12 days after intratumoral injection of bloodroot extract. Notice the distinct margin between the neoplasm (left side of the image) and an area of epidermal and dermal necrosis with early granulation tissue formation (right side of the image). The neoplasm appears to be intact and unaffected by the adjacent tissue necrosis. H&E stain; bar = 500 µm.

The excised mass was submitted in toto for histologic examination. Histologically, the mass was comprised of ribbons of epithelial cells with the morphology of basilar epithelial cells. Mitotic activity among neoplastic cells was low. Morphologically, the mass was identified as an ulcerated trichoblastoma (basal cell tumor). The mass was well circumscribed, and surgical excision of the neoplasm appeared to be complete. Immediately adjacent to the dermal neoplasm was a localized area of coagulative necrosis of the dermis and overlying epidermis (**Figure 3**) with a peripheral zone of neovascularization and fibroplasia (granulation tissue).

The dog was discharged to the owner's care the same day that surgery was performed. Cephalexin (25 mg/kg, PO, q 12 h), carprofen (4 mg/kg, PO, q 24 h), and tramadol (4 mg/kg, PO, q 8 to 12 h) were prescribed postoperatively. The dog was reexamined 2 weeks after excision of the tumor. At this time, the surgical scar appeared to be healing well, and skin sutures were removed. There was no evidence of tumor recurrence or ongoing tissue injury. The dog was discharged to the owner's care with instructions to monitor the surgical site for delayed wound dehiscence or other postsurgical complications. The dog was doing well with no postsurgical complications at the time of this report.

Discussion

Medicinal preparations containing bloodroot extract are often called escharotics owing to their ability

to elicit inflammation, necrosis, and subsequent eschar formation following contact with living tissues.[1,2] Both of the dogs described in the present report were treated with an escharotic agent via intratumoral injection. One of these dogs had a dramatic necrotizing inflammatory reaction of the subcutaneous tissues following injection, resulting in the formation of a cavitated necrotic lesion approximately 50 times the size of the original tumor. The large size of the necrotic lesion necessitated extensive surgical treatment, whereas prior to injection, marginal excision of the tumor would likely have been curative. Moreover, this dog developed multiple complications, including seroma formation, wound infection, and wound contracture, following removal of the necrotic lesion that prolonged wound healing and hampered mobility. Whether these postsurgical complications were related to patient factors, surgical factors, bloodroot extract treatment, or a combination thereof could not be ascertained.

Curiously, there was a marked difference in the tissue reaction to injection of bloodroot extract between dog 1 and dog 2. Examination of tissues excised from dog 1 demonstrated extensive necrosis of the dermis and subcutis surrounded by abundant granulation tissue. Similar findings of dermal necrosis and granulation tissue formation were present in the tissues excised from dog 2, but these pathological changes were much less severe and were sharply demarcated from nearby neoplastic tissue. The reason for the disparity in these reactions is unknown. One possible explanation is that the drug was poorly retained in dog 2 following injection, in that the owner noticed an oily substance leaking from the tumor shortly after injection. If this was the case, then the smaller amount of active drug retained in the tumor could have been expected to elicit a relatively weaker biological effect. The disparity in reactions may also have been related to differences in dose volume. Dog 2 received a smaller dose of bloodroot extract than did dog 1, and this smaller dose may also have contributed to the relatively milder tissue reaction. Substandard manufacturing practices may also explain the disparate tissue reactions in these 2 dogs. The product used in these dogs has not been approved by the US FDA for use in people or animals, and to our knowledge, there has been no independent confirmation of its purity or potency. Thus, distribution of biologically active compounds within the product may be haphazard or uneven. It is, therefore, possible that the concentration of active drug in the dose given to dog 1 was greater than the concentration in the dose given to dog 2.

Bloodroot and other escharotic agents have a long history of medicinal use. Reports on the use of bloodroot-based escharotic salves by Native Americans for the topical treatment of wounds, infections, and cutaneous tumors date to the time of European colonization of the Western hemisphere.[2] Frederic Mohs is credited with introducing escharotics to Western medicine in the 1930s. Mohs applied a paste containing bloodroot, antimony trisulfide, and zinc chloride as an in vivo tissue fixative prior to surgical excision of cutaneous tumors.[3] This procedure allowed rapid sectioning and histologic examination of tumors to determine completeness of excision. If tumor cells were detected at the surgical margins, the process of paste application and excision was repeated daily until microscopically complete excision was achieved, at which point the surgical wound was closed. Drawbacks to Mohs' technique were that it was painful, was destructive to healthy tissue as well as tumor tissue, and precluded immediate closure of the surgical wound. Mohs' technique for the removal of cutaneous neoplasia has largely been abandoned with the advent of fresh-frozen tissue sectioning in the 1970s.[2]

Several Internet sites promote the use of bloodroot and other escharotics[a,f,g] as topical, parenteral, and oral preparations for the treatment of cutaneous neoplasia. In contrast to the methodology advanced by Mohs, the manufacturers of these products do not advocate surgical removal and histologic examination following escharotic treatment. The author of 1 such Internet site,[4] for example, claims that "biopsy is an unnecessary procedure…because little useful information is resultant from biopsy."[4] In most cases, these Internet sites advocate the use of bloodroot, often in the form of a topical salve, as a primary treatment for cutaneous tumors. Information regarding tumor response to escharotic treatment is usually limited to testimonials that are uniformly positive in nature.

Although proponents of bloodroot provide extensive testimonial accounts of its antitumor efficacy, the molecular mechanisms of its cytotoxic effects are unclear. Bloodroot contains several alkaloids that may have cytotoxic activity, including sanguinarine, chelerythrine, protopine, and others.[5] Of these compounds, sanguinarine has received the most attention. In vitro, sanguinarine has many biological effects that may confer antineoplastic activity. Sanguinarine-mediated apoptosis has been demonstrated in numerous human cancer cell lines,[6] and in 1 study,[7] sanguinarine induced cell cycle arrest in a human prostatic carcinoma cell line by several mechanisms, including induction of the cyclin-dependent kinase inhibitors $p21^{Waf1/Cip1}$ and $p27^{Kip1}$; downregulation of cyclins D1, D2, and E; and downregulation of cyclin-dependent kinases 2, 4, and 6. Sanguinarine is also a potent inhibitor of the mitogenic and antiapoptotic transcription factor NF-κB.[8]

The cytotoxic effects of sanguinarine may be different in healthy cells and neoplastic cells. Ahmad et al[9] showed that sanguinarine induces apoptosis in neoplastic human keratinocytes at concentrations (1 to 2μM) lower than those necessary to elicit biological effects in normal keratinocytes. This observation has been cited by some proponents of bloodroot-based products as evidence that such products preferentially injure neoplastic cells while having no harmful effects on normal cells.[4] To the authors' knowledge, such a conclusion has never been demonstrated in vivo, and the consequences of bloodroot administration in the dogs described in this report absolutely refute it. Moreover, those who are proponents of bloodroot's selective effects on neoplastic cells because of the findings of Ahmad et al[9] ignore the fact that these investigators demonstrated significant necrosis of normal keratinocytes following exposure to higher concentrations (2 to 5μM) of sanguinarine. Whether such concentrations can be achieved in vivo with topical or intratumoral administration of bloodroot is unknown.

Although the cytotoxic properties of sanguinarine in vitro are intriguing, the authors are unaware of published results from well-designed clinical trials in humans or domestic animals that document the efficacy of sanguinarine or crude bloodroot extracts as antineoplastic agents. There is limited information in the veterinary medical literature regarding the use of bloodroot-based products in domestic animals. Anecdotal reports on the use of 1 particular product[f] for treatment of cutaneous neoplasia in horses have been published,[10,11] but experimental data on tumor response are lacking. To our knowledge, there are no published reports concerning the use of such products in dogs. However, several published case reports[1,2,12–16] describe the harmful effects of bloodroot and other escharotics in the treatment of cutaneous neoplasia in people. In most of these cases, the primary adverse effects were cosmetic and not life threatening and included scarring and anatomic deformation. However, in some cases, the degree of cosmetic disfigurement was severe. Many patients also reported localized pain after application of escharotic salves. Of most concern, there is a report[16] of a 52-year-old man who developed a deeply invasive recurrent basal cell carcinoma over the left nasal ala after escharotic treatment of a primary basal cell carcinoma at that site approximately 8 years previously. Despite aggressive surgical resection of the recurrent tumor, this patient went on to develop nodal and visceral metastases, which ultimately resulted in his death. Whether bloodroot contributed to the malignant progression of this tumor cannot be determined. However, given the well-documented propensity for bloodroot to elicit localized inflammation and the potential for inflammation to promote cancer progression,[17] such a possibility cannot be discounted. Bloodroot or sanguinarine has also been associated with oral leukoplakia following gingival application,[18] a systemic capillary leakage syndrome following oral administration,[19] and cardiotoxicosis.[20]

The adverse reaction to bloodroot administration seen in dog 1 emphasizes the responsibility that veterinarians have when prescribing herbal treatments and in discussing these treatments with clients. Herbal products and other unconventional treatments are commonly used by human cancer patients, with 1 survey finding that 83.3% of respondents had used some form of treatment not prescribed by a physician.[21] Vitamins and herbal products were the second most commonly used type of nonprescribed treatment in this patient population, with 62.6% of survey respondents reporting their use. Many users of unconventional treatments do not discuss them with their physicians. Eisenberg et al[22] reported that 72% of all patients employing some form of unconventional treatment did so without a physician's knowledge. A survey done by Lana et al[23] showed similar trends in veterinary oncology. In this survey of 254 owners of dogs or cats receiving treatment by a veterinary oncologist, 76% of respondents reported using some form of unconventional treatment. Herbal and botanical products were the sixth most commonly used treatment. Fifty-seven percent of respondents said that they had not discussed the use of these treatments with a veterinarian.

These survey results indicate that veterinarians should be aware of the popularity of herbal treatments among owners of pets with cancer. As with any drug, veterinarians are responsible for familiarizing themselves with the indications, appropriate dosage, potential for drug interactions, and possible adverse effects of herbal products before recommending or condoning their use. Although such information is often difficult to find, several good references are available.[24–26] Consultation with a veterinary oncologist or veterinary pharmacologist may also be of benefit. Moreover, veterinarians should be willing to engage pet owners in open dialogue about the use of herbal products. A dismissive or condemnatory approach should be avoided as it may be offensive or embarrassing to pet owners and discourage further communication. Rather, a compassionate and reasoned approach may facilitate proper use of herbal products and discourage pet owners from using those products that are potentially harmful.

The authors believe that bloodroot and other escharotics constitute potentially harmful herbal products, and that their use in the treatment of cutaneous neoplasia in domestic animals should be discouraged. This recommendation is based on several factors. First, escharotics may be manufactured without regard to accepted standards and therefore may contain unknown quantities of pharmacologically active compounds or toxic adulterants.[1] Second, in the absence of biopsy prior to escharotic administration, escharotic treatment precludes accurate histologic identification of tumor type. Third, escharotic treatment prevents accurate in vivo or histologic assessment of tumor margins. This is particularly important for invasive tumors of the skin and subcutis, such as mast cell tumors, soft tissue sarcomas, and injection site sarcomas. Inadequate evaluation of tumor margins may result in cancer recurrence, possibly accompanied by more aggressive tumor behavior. Fourth, escharotic treatment is painful and cosmetically unappealing. Fifth, escharotic treatment has no documented history of success in the human or veterinary medical literature. Sixth, escharotic treatment may be unnecessary. Reportedly, 54% to 63% of canine cutaneous tumors,[27,28] 34% to 39% of feline cutaneous tumors,[27,29] and 22% to 93% of equine cutaneous tumors[27,30,31] are benign and do not require aggressive treatment. Finally, and most importantly, escharotic administration may delay or prevent definitive treatment by a more effective means, notably surgical excision, which is curative for many cutaneous tumors.

As documented clinically and histologically in the dogs described in this report and as demonstrated in many reports in the human medical literature, bloodroot and other escharotic products have the potential to do harm if administered topically or intratumorally to treat cutaneous neoplasia. These agents have no place in the treatment of human skin cancer, and Frederic Mohs, the introducer of escharotics to Western medicine, in 1948 publicly condemned their use without accompanying surgery because they were ineffective and disfiguring.[32] The US FDA has issued warning letters to several purveyors of escharotics, including companies distributing products for use in domestic animals, on the grounds that these products are marketed as drugs for treatment of specific medical conditions, but have not been proven efficacious or safe.[33] Veteri-

narians should be aware of the potential deleterious consequences of escharotic administration and should likewise discourage clients from using escharotics on their animals until indications for their use, appropriate dosages, and incidences and types of adverse effects are established in well-designed clinical trials.

a. NeoplaseneX with methyl sulfoxide, Buck Mountain Botanicals Inc, Miles City, Mont.
b. Dasuquin, Nutramax Laboratories Inc, Edgewood, Md.
c. MSM, Biotics Research Corp, Rosenberg, Tex.
d. Wild Alaska Salmon Oil, Alaska Protein Recovery LLC, Juneau, Alaska.
e. Arnica 30C Pellets, Boiron, Newton Square, Pa.
f. XXTerra, Larson Laboratories, Fort Collins, Colo.
g. Veterinary Cansema Black Salve mix, The Original Cream Co, Magnolia, Ark.

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