Herbs for Animal End-of-life and Palliative Care

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Abbreviations

COX-2	Cyclooxygenase-2
IL	Interleukin
iNOS	Inducible nitric oxide synthase
NF-κB	Nuclear factor kappa B
TNF-α	Tumor necrosis factor-α
Treg cell	Regulatory T cell

Abstract

The use of specific herbal treatments to support animal patients nearing the end of their life is expanding as more attention is given to hospice and palliative care. A literature review of some of the most commonly used herbs was conducted to address their specific actions and available evidence for their benefit to these patients. Herbs reviewed include ashwagandha (*Withania somnifera*), ginger (*Zingiber officinale*), chamomile (*Matricaria recutita*), calendula (*Calendula officinalis*), marshmallow (*Althaea officinalis*), and licorice (*Glycyrrhiza glabra*).

Introduction

End-of-life care is growing in importance in veterinary medicine as owners and clinicians seek better ways to improve quality of life through pain management and palliation. Decisions for treatment and care vary greatly among caregiving families and are based on their own life experiences, limitations, and opportunities. As veterinarians, we are best positioned to offer education about signs of animal discomfort and distress, disease progression, prognosis, and treatment options. When a cure is no longer likely, palliative or comfort care is often a welcome option as patients near the end of their life. There are many possibilities for comfort care, including environmental adaptations such as padded bedding, ramps, steps, or carpet runners covering slick floors as well as medications for pain, nausea, or respiratory distress. Our clients may have different preferences for treatments, and our patients may have varying needs. A team approach helps to keep treatment options open, and referrals among colleagues can be used when a different approach is needed or desired.

Concerns have been voiced from conventional practitioners that the use of complementary therapy may delay needed treatments and increase animal suffering. Awareness of all potential therapeutic options and timely recognition of clinical signs of pain and discomfort in animals can help to allay these concerns. Often complementary therapies, especially when instituted early in the disease process, can improve the comfort of our animal patients and reduce the need for pharmaceutical and other more aggressive treatments that might be less than ideal for fragile patients nearing the end of life. Herbal medicine is 1 of many treatment possibilities for animal end-of-life and palliative care and can be used in combination with other therapies, complementary and conventional, including most pharmaceutical drugs, especially when pain management is an issue.

Clinical Signs of Discomfort

In animals, we have the legal and often welcome option of euthanasia for patients reaching the end of life and showing signs of discomfort or distress. We also have a wide array of treatment modalities to allay this discomfort, delaying or even eliminating the need for euthanasia. Palliative care can allow patients to continue to live longer with an improved quality of life (1). In animal hospice, clinical signs of discomfort often become a larger concern than the underlying disease process, though both should be taken into account along with the animal's individual needs. Early initiation of palliative treatments is important for preemptive management and avoidance of crisis situations. This is an area where herbal medicine can be especially beneficial in patient care.

Some of the most concerning signs seen in animals include pain, respiratory distress, anxiety, seizures, nausea, vomiting, diarrhea, bleeding, and skin lesions. Herbal medicine can address many of these issues through multiple pathways of action. A survey of veterinary herbal practitioners from around the world revealed the multitude of herbal treatment options used for these varying conditions (a):

Pain: corydalis (*Corydalis yanhusuo*), meadowsweet (*Filipendula ulmaria*), willow (*Salix alba*), pukatea (*Laurelia novae-zelandiae*), cramp bark (*Viburnum opulus*), valerian (*Valeriana officinalis*), cannabis (*Cannabis sativa*), black cohosh (*Actaea racemosa*), black haw (*Viburnum prunifolium*), Indian pipe (*Monotropa uniflora*), Jamaica dogwood (*Piscidia erythrina*), noni (*Morinda citrifolia*)

Gastrointestinal conditions including vomiting, diarrhea, ulcers, motility disorders, fecal incontinence: marshmallow (*Althea officinale*), meadowsweet (*Filipendula ulmaria*), licorice (*Glycyrrhiza glabra*), fennel (*Foeniculum vulgare*), flax seed (*Linum usitatissimum*), blackberry (*Rubus fructicosis*), ginger (*Zingiber officinale*), chamomile (*Matricaria recutita*), slippery elm (*Ulmus fulva*), agrimony (*Agrimonia eupatoria*), green tea (*Camellia sinensis*), boldo (*Peumus boldus*), dandelion (*Taraxacum officinale*), papaya (*Carica papaya*), plantain (*Plantago major*), bupleurum (*Bupleurum falcatum*), psyllium (*Plantago ovata*)

Renal/urinary conditions including renal disease, bladder infection, incontinence, atony: milk thistle (*Silybum marianum*), crataeva (*Crataeva nurvala*), uva ursi (*Arctostaphylos uva-ursi*), rehmannia (*Rehmannia glutinosa*), marshmallow (*Althea officinale*), cranberry (*Vaccinium macrocarpon*), cornsilk (*Zea mays*), dandelion (*Taraxacum officinale*), buchu (*Agathosma betulina*), chanca piedra/ stonebreaker (*Phillanthus niruri*)

Respiratory conditions including dyspnea, upper and lower respiratory signs: marshmallow (*Althea officinale*), white horehound (*Marrubium vulgare*), licorice (*Glycyrrhiza glabra*), echinacea (*Echinacea spp.*), thyme (*Thymus vulgaris*), mullein (*Verbascum thapsus*), elder (*Sambucus nigra*), lobelia (*Lobelia inflata*), bloodroot (*Sanguinaria canadensis*), Seneca snakeroot (*Polygala senega*), sundew (*Drosera rotundifolia*, *D. angelica*, etc.)

Cardiovascular conditions including tachycardia, bradycardia, hypertension, hypotension, bleeding: hawthorn (*Crataegus spp.*), motherwort (*Leonurus cardiaca*), lemon balm (*Melissa officinalis*), astragalus (*Astragalus membranaceus*), garlic (*Allium sativum*), yarrow (*Achillea millifolium*), lily of the valley (*Convallaria majalis*), valerian (*Valeriana officinalis*)

Musculoskeletal conditions including arthritis, muscle tension, pain: boswellia (*Boswellia serrata*), gotu kola (*Centella asiatica*), cramp bark (*Viburnum opulus*), devil's claw (*Harpagophytum procumbens*), Solomon's seal (*Polygonatum biflorum*), turmeric (*Cucurma longa*), ginger (*Zingiber officinale*), yucca (*Yucca spp.*), valerian (*Valeriana officinalis*), cat's claw (*Uncaria tomentosa*)

Dermatological conditions such as decubitus ulcers: comfrey (*Symphytum officinale*) topically, calendula (*Calendula officinalis*), chamomile (*Matricaria recutita*), green tea (*Camellia sinensis*), plantain (*Plantago major*), burdock (*Arctium lappa*), schisandra (*Schisandra chinensis*), gotu kola (*Centella asiatica*), orange ball (*Buddleja globosa*), aloe (*Aloe vera*), noni (*Morinda citrifolia*), echinacea (*Echinacea spp.*)

Neurological including seizures, cognitive dysfunction, restlessness, anxiety: bacopa (*Bacopa monnieri*), skullcap (*Scutellaria lateriflora*), passionflower (*Passiflora in-*

carnata), valerian (*Valeriana officinalis*), catnip (*Nepeta cataria*), oats (*Avena sativa*), gingko (*Ginkgo biloba*), gotu kola (*Centella asiatica*), Saint John's wort (*Hypericum perforatum*), Solomon's seal (*Polygonatum biflorum*), alfalfa (*Medicago sativa*), hops (*Humulus lupulus*)

As can be seen by this survey, there are many possible herbal choices and much overlap in effect for various clinical signs of concern. Herbs are chosen for different purposes in individual cases. For example, herbs for pain may be chosen for additional properties such as anti-inflammatory, anti-anxiety, or muscle relaxation.

A literature review using PubMed and the Natural Medicines database was conducted to provide an overview of a small assortment of commonly used herbs in palliative care. Many botanicals used therapeutically for geriatric medicine have unique qualities of enhancing the immune system as well as general cell and organ function through multiple pathways. The focus of this review is on herbal actions and their potential benefits for the palliation of clinical signs that may cause discomfort in animal patients.

Ashwagandha (*Withania somnifera*)

Ashwagandha has been used in Ayurvedic medicine for thousands of years, especially in geriatric and malnourished patients, as an overall tonic to support general body functions and to build strength and vitality. It is known for anti-inflammatory, antioxidant, anti-neoplastic, immunomodulatory, anti-anxiety, and stress protective actions, among others, and has been found anecdotally by clients to make their animals feel better and have more energy (2). Ashwagandha is considered an adaptogen in herbal medicine, meaning it helps the body to adapt to physical, emotional, and environmental stress, supports normal metabolic functions including the endocrine and immune systems, and is non-toxic and safe for long-term use (2, 3). At very high doses, ashwagandha can cause abortion and gastrointestinal discomfort including diarrhea or vomiting, and it may potentiate the effects of sedative and anxiolytic medications (2). Ashwagandha is used as a general supportive herb in geriatric patients and those nearing the end of life, especially those having osteoarthritis, neoplasia, inflammatory conditions, anxiety, and general debilitation.

Anti-Inflammatory, Antioxidant, Organoprotective, and Antineoplastic Effects

Several molecular targets have been identified to explain ashwagandha's actions in vivo, particularly the anti-inflammatory, antioxidant, antineoplastic, and immunomodulatory effects. The steroidal lactone withanolide, withaferin A, is an important constituent that is commonly studied. In vitro studies have shown withaferin A to inhibit nuclear factor kappa B (NF-κB) activation, and in various cancer cell lines to induce apoptosis, inhibit angiogenesis, and inhibit cell proliferation (4). Chronic inflammatory diseases can activate the NF-κB pathway, and withaferin A was found to block this pathway by modulation of cellular thiols thereby inhibiting T-cell and B-cell activation, proliferation, and function, in turn reducing the production of inflammatory cytokines (5).

In addition to having antineoplastic activities, ashwagandha acts to protect organ function. When used as a pretreatment adjunctive therapy for radiation in rats, it was protective against hepatotoxicity caused by oxidative stress and enhanced upregulation of liver-protective heme oxygenase–1 (6). Gentamicin-induced renal toxicity in rats was reversed significantly, with the most effective dose found to be 500 mg/kg (7).

Musculoskeletal Support

In an 8-week randomized, double-blind, placebo-controlled clinical study, human patients with knee joint pain and discomfort were significantly improved with twice daily dosages of 125 mg and 250 mg of a standardized aqueous extract of ashwagandha root and leaves as compared to a placebo. There was a significant dose-related improvement of scores for knee swelling, pain, stiffness, disability, time to effect, and use of rescue pain medication (8).

In a randomized controlled trial of healthy human weightlifting subjects, ashwagandha was found to significantly increase muscle mass and strength while decreasing serum creatine kinase caused by muscle injury compared to a placebo group (9). Along with its many supportive benefits, this may indicate an additional use of ashwagandha for geriatric patients with muscle loss.

Anti-Anxiety Effects

Ashwagandha was shown in a prospective, randomized, double-blind, placebo-controlled study to reduce stress and anxiety in human patients with a history of chronic stress by significantly reducing blood cortisol levels as well as clinical signs measured in stress-assessment scales (10).

Ginger (*Zingiber officinale*)

Ginger root, along with turmeric and other food-based herbs, has been found to have significant anti-inflammatory and antioxidant actions, and has caught the attention of the mainstream medical profession. These plants are often recommended as dietary additions due to their safety, effectiveness, and palatability. For our animal patients, ginger has been used for its anti-inflammatory effect, as an antiemetic for cancer, renal disease, and other conditions, as a neuroprotective in cognitive decline, as well as a circulatory stimulant, and a general warming herb for patients that are affected by colder temperatures or poor circulation. Ginger is a hot, spicy herb and can cause excessive body heat or heartburn at higher doses.

Musculoskeletal Support

In a randomized, double-blind, placebo-controlled clinical trial, human patients with knee osteoarthritis were supplemented with 500 mg ginger root twice daily for 3 months and found to have decreased serum levels of proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β as compared to the placebo group (11). A parallel study also found decreases in the inflammatory indicators nitric oxide and C-reactive protein in serum samples after 3 months of supplementation with ginger (12). TNF-α and IL-1 are mediators in the induction of NF-κB, which activates inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and lipoxygenase pathways to produce nitric oxide, prostaglandins, and leukotrienes, thereby causing inflammation. This inflammatory process is inhibited by gingerols and shogaols, phenolic compounds found in ginger (13).

Gastrointestinal Support

The anti-inflammatory action of ginger has been studied in vitro to understand its use as a gastrointestinal barrier protectant. 6-Shogaol, a commonly studied constituent of ginger, was found to inhibit a barrier disturbance induced by TNF-α, to inhibit signaling of phosphatidylinositol-3-kinase/Akt, and to inhibit the induction of NF-κB (14). Ginger has been studied extensively as an anti-nausea agent, especially in human chemotherapy patients, who may have significant discomfort. Some studies show significant benefits, while others have mixed results; this may be affected by timing of delivery, dosage, and quality of products used (15). In Western herbal formulations, ginger is given on a daily basis and may potentially reduce the onset of nausea by having consistent ongoing anti-inflammatory action.

Cognitive Support

Studies have shown ginger to have a positive effect on cognitive function and a potential use in human patients with dementia. Animal patients with cognitive decline may also benefit. Administration of 6-shogaol was found to significantly reduce microgliosis and astrogliosis in laboratory mice with induced memory impairment, indicating a role in the inhibition of glial cell activation to reduce the damage of chronic CNS inflammation which leads to cognitive decline (16). In addition to the anti-inflammatory effects, ginger has also been shown to significantly improve learning and memory in mice. A ginger extract given to the studied mice increased behavioral recognition of novel objects while increasing nerve growth factor levels in the hippocampus, which led to activation of the extracellular-signal-regulated kinase and cyclic AMP response element-binding protein signaling pathway. Significant increases in pre- and post-synaptic markers also suggested a rise in synapses in response to the administration of ginger extract (17).

Respiratory Support

Ginger tea is used for respiratory conditions as a cough suppressant and for its anti-inflammatory effect. Oral dosages of 25 and 50 mg/kg hot water ginger extract containing primarily polysaccharides significantly reduced cough reaction in laboratory guinea pigs (18). Ginger may also be helpful in cases of asthma and other inflammatory lung conditions. In a recent study in mice with induced inflammatory lung disease, doses of ethanolic (500 mg/kg/day) and aqueous (720 mg/kg/day) ginger root extracts were compared to methylprednisolone (5 mg/kg/day) along with positive (untreated

inflammatory) and normal controls (19). Both ginger extracts significantly reduced the presence of inflammatory cells in blood and histopathology samples of the mice to a similar degree as the methylprednisolone and appeared to inhibit the helper T cell 2-mediated immune response indicated by decreased levels of mRNA expression of the cytokines IL-4 and IL-5. An in vitro study demonstrated a relaxant effect on airway smooth muscle tissues, which in vivo would cause bronchodilation, improving respiratory comfort (20). The isolated constituents of ginger, 6-gingerol, 8-gingerol, and 6-shogaol were effective in causing rapid relaxation of the muscle tissues, though 10-gingerol did not have this effect. The modulation of intracellular calcium appears to play a part in the mechanism of action. In a randomized, controlled, double-blinded clinical study, human patients in an intensive care setting with acute respiratory distress syndrome were given an enteral diet supplemented with 120 mg ginger extract divided daily into feedings, while control subjects were given 1g coconut oil as a placebo. The patients supplemented with ginger extract in their diet experienced significant improvements including increased oxygenation levels, reduced inflammatory markers (serum IL-1, IL-6, TNF-α, and leukotriene B4), reduced time on mechanical ventilation, and reduced stay in the intensive care unit (21).

Chamomile (*Matricaria recutita*)

Chamomile is 1 of the most common herbal remedies used regularly and safely around the world and is readily available as a tea. Like many phytotherapeutics, chamomile is known for its anti-inflammatory and antioxidant properties. It also has recognized antispasmodic, carminative, relaxant, and anxiolytic actions (2). It is primarily used for gastrointestinal, oral, and dermatological inflammation along with its calming effect as a bedtime tonic. In palliative care it can be beneficial for anxiety, restlessness, gastrointestinal distress, ulcers, oral lesions, gingivitis, skin irritation, and pressure sores.

Anti-Inflammatory and Antioxidant Effects

In multiple in vitro studies using macrophages, various anti-inflammatory and antioxidant activities of chamomile extracts have been identified. The inhibition of COX-2 enzyme activity reducing the release of lipopolysaccharide-induced prostaglandin E(2) was shown, as well as the inhibition of IL-1β, IL-6, TNF-α, lipopolysaccharide-induced NO production, and iNOS mRNA and protein expression (22, 23). Willow bark (*Salix alba*), meadowsweet (*Filipendula ulmaria*), and chamomile herbal extracts all reduced IL-6 and TNF-α production in macrophages in vitro (24).

Cytoprotective actions of chamomile were shown through the induction of antioxidant enzymes including nicotinamide adenine dinucleotide phosphate, quinone oxidoreductase, superoxide dismutase, and catalase, and the increase and activation of the transcription factor Nrf2 in cell nuclei (25).

The flavonoid apigenin, an important chemical constituent of chamomile, passionflower (*Passiflora incarnata*), and many fruits and vegetables, has shown anti-inflammatory action through the suppression of NF-κB pathway activation and thereby inhibition of inflammatory factors COX-2, reactive oxygen species, intercellular adhesion molecule-1, IL-6, and IL-8 (26).

Gastrointestinal Support

Chamomile has been found to have effects against the pathogenic gastrointestinal bacterium *Helicobacter pylori* both in vitro and in vivo (27). Apigenin was found, at a dose of 60 mg/kg, to significantly decrease *H. pylori* colonization and inflammatory stomach changes including neutrophil and monocyte infiltrations in Mongolian gerbils, significantly reducing atrophic gastritis and gastric cancer progression (28). Although the significance of *H. pylori* infection in dogs and cats is uncertain, the gastrointestinal anti-inflammatory effects of chamomile may benefit our animal patients.

Chamomile infusion exhibited a gastroprotective effect in vitro by inhibiting the up-regulation of neutrophil elastase and matrix metalloprotease-9 (29). These enzymes are involved in the degradation of the extracellular matrix and cell basement membranes in inflammation, tumor metastasis, and other processes involving tissue remodeling. The chamomile infusion acted, at least in part, through the inhibition of the NF-κB pathway, which is active in chronic inflammation. The gastroprotective effect of chamomile extract was shown in rats with ethanol-induced gastric mucosal injury (30). Treatment was given 1 hour prior to the administration of high dose ethanol; and although chamomile was effec-

tive at all doses, a 200 mg/kg dose showed the most significant protection, at a level similar to famotidine.

Anti-Anxiety Effects

Multiple flavonoids, including apigenin, have been found to affect the activation of inotropic receptors for gamma-aminobutyric acid (an important inhibitory neurotransmitter) similar to benzodiazepine drugs, with resulting cognitive improvement, lessened anxiety, and sedative effects (31). In randomized placebo-controlled clinical trials of human patients with generalized anxiety disorder, chamomile extract given at a dose of 1500 mg daily produced a response rate comparable to treatments with conventional anxiolytic drugs. Short-term (8-week) and long-term (38-week) treatments demonstrated a significant reduction in moderate to severe signs of anxiety with few mild adverse events, indistinguishable from the placebo (32, 33).

Calendula (*Calendula officinalis*)

The flowers and aerial parts of calendula are known primarily for their topical wound-healing activity. This, in conjunction with antiseptic, anti-inflammatory, and antineoplastic properties, makes calendula especially useful for dermatological conditions including decubitus ulcers, inflammatory and infected wounds, ulcerating skin tumors, and collateral damage from radiation therapy (34). Due to the potential for rapid dermal closure, use of calendula is recommended with caution in deep wounds where drainage must be kept open as deeper tissue healing occurs. Calendula flower extractions are used orally for gingivitis, periodontal disease, and in oral cancers to reduce discomfort due to pain, inflammation, and infection. Oral ingestion as a tea and in other forms has shown benefits for the lymphatic, hepatic, renal, pancreatic, and other systems as well as reducing blood triglycerides, though research in these areas is not as prevalent as it is for wound healing (2, 35).

Anti-Inflammatory and Antioxidant Effects

As with most herbs, multiple chemical constituents are involved in the anti-inflammatory and antioxidant actions of calendula. The antioxidant activity of calendula is seen even in low doses of flavonoids, (quercetin, protocatechuic acid), and carotenoids (B-carotene, lycopene). Calendula flower extract was shown to have significant anti-inflammatory action against experimentally induced acute and chronic paw edema in mice at oral doses of 250 and 500 mg/kg (36). Systemic levels of pro-inflammatory cytokines IL-1s, IL-6, TNF-α, interferon gamma, acute phase protein, C-reactive protein, and COX-2 were significantly reduced in mice with induced inflammation. In vitro, calendula extract significantly inhibited TNF-α production by macrophages treated with an inflammatory agent (37). Multiple chemical constituents of calendula, particularly triterpene glycosides, were found to have anti-inflammatory, anti-tumor promoting, and cytotoxic activity indicating further use in the treatment of neoplasia.

Wound Healing Effects

An ethyl alcohol extract of calendula was found to stimulate the proliferation and induce the migration of fibroblasts in vitro by acting on the PI3K pathway, a signaling pathway for the directional migration of corneal and skin epithelial cells during healing following injury (38). Chemical constituents that may be active in this process include esculetin, a coumarin compound, and the flavonoid quercetin (39). Increased expression of proteins involved in the granulation phase of wound healing, connective tissue growth factor, and α-smooth muscle actin occurred in vivo after application of ethanol and water extractions of calendula (40). Treated mice also showed significantly faster wound healing than control groups. Rutin and quercetin-3-O-glucoside were the major active compounds identified, and the water fraction in these experiments appeared to be more effective than ethanol extractions.

Gingivitis/Oral Care

Animal hospice patients often suffer from dental disease due to a reluctance to have fragile animal patients anesthetized for dental cleaning. Ideally, dental care would occur throughout the aging years to minimize problems, but this does not always occur. As the end of life approaches, alternatives to more invasive procedures are explored. Calendula has been used for oral care in human and animal patients with gingivitis and accumulation of dental plaque. A study of human patients in India found a significant reduction of gingival inflammation and plaque formation using a recommended twice daily mouthwash consisting of 2 ml calendula tincture mixed with 6 ml distilled water when compared to a placebo mouthwash (41). A similar wash can be used

in animals as a tea added to drinking water or administered by syringe. The flavor is generally pleasant, but care should be taken not to affect the patient's overall water intake. An oral wash of calendula tea may also be beneficial to patients with oral tumors or wounds due to the antiseptic and wound-healing properties discussed earlier. A mouthwash made of combined extracts from ginger, rosemary (*Rosmarinus officinalis*), and calendula was compared to chlorhexidine in a randomized, double-blind, placebo-controlled trial of patients with gingivitis and found to have similar benefits (attributed to the combined antimicrobial and anti-inflammatory effects of those herbs), making this a safe and effective alternative when needed or desired (42).

Gastrointestinal Support

Calendula has been found to improve wound healing within the gastrointestinal tract as well. Experimentally induced ulcerative colitis in rats treated with oral and rectal calendula extract (3000 mg/kg orally; 20% gel enema) had similar results to the drug mesalamine used for treating inflammatory bowel disease in humans (43). Significant weight gain, reduction of inflammation, and histopathological signs of healing were seen compared to negative control groups.

Marshmallow (*Althaea officinalis*)

Marshmallow is a mucilaginous plant, high in flavonoids and polysaccharides, whose roots and occasionally leaves are used medicinally (2). Its primary role is in soothing mucous membranes of the gastrointestinal and respiratory tracts, though marshmallow has also been used in conjunction with other herbs for urinary tract infection and inflammation, in oral washes for periodontal disease, and as a topical wound treatment. Generally considered very safe, contraindications are limited to the theoretical potential to interfere with absorption of medications given concurrently.

Respiratory Support

Marshmallow root is commonly used as a cough suppressant, with its action assumed to be due to direct relief of irritated mucosa by adhesion of the mucilaginous material. It has been found to stimulate the cellular physiologic activity and proliferation of epithelial KB cells to facilitate healing (44). Polysaccharides of marshmallow root at a dose of 100 mg/kg were shown to have cough suppressant effects similar to that of prescription cough medicines including codeine (45). The polysaccharide rhamnogalacturonan was found to have a cough suppressive effect associated with 5- hydroxytryptamine 2 serotonergic receptors (46).

Aqueous and methanol extracts of marshmallow root were shown to cause dose-dependent bronchodilation by reducing tracheobronchial smooth muscle contraction in vitro (47).

Wound Healing

Marshmallow leaf extract was shown to be effective against gram-positive bacteria and to benefit wound healing through anti-inflammatory and antioxidant effects attributed to phenolic acid and flavonoid constituents (48). Antioxidant effects against DNA damage were shown, with marshmallow root extract demonstrating protective effects against indirect UVA-induced oxidative stress, though not against full spectrum UVA and UVB irradiation (49).

Licorice (*Glycyrrhiza glabra*)

Licorice root is often considered in Western veterinary herbal medicine to be the herbal steroid equivalent. As such, it has a few more safety considerations than the other herbs discussed here. These side effects are minimal compared to its pharmacological cousin, however, in part because of the many protective constituents also present in the plant. The major chemical constituent of licorice root, glycyrrhizin (glycyrrhizic acid), a triterpene saponin, has been studied most extensively and is responsible for the dose-dependent mineralocorticoid-like effects of licorice root. In people, high dose intake of licorice candy (when made with real licorice root) and licorice root used as medicine led to pseudohyperaldosteronism with signs of hypertension, edema, and hyperkalemia that resolved with removal of licorice from the diet (50). Low dose licorice use has been found to be safe long-term. In a review of risks and safety assessments, a safe low dose range for glycyrrhizin in mice and rats was determined to be 15–229 mg/kg/day (51).

In addition to triterpenoid saponins, licorice contains multiple flavonoids, coumarins, and other constituents that contribute to its beneficial actions which include anti-inflammatory, antioxidant, antiviral, antimicrobial,

antineoplastic, immunomodulatory, gastroprotective, hepatoprotective, neuroprotective, and cardioprotective (52). Because of the organo-supportive effects in combination with the steroidal actions, licorice root has been used as a replacement and as an adjunct to pharmacologic steroid treatment and may be helpful in lowering steroid dose while maintaining patient comfort.

Hepatoprotective, Anti-Inflammatory, and Antioxidant Effects

Licorice root is commonly found in small amounts in many Traditional Chinese Medicine herbal formulas and digestive tea blends. Known as the "universal harmonizer," it appears to have synergistic and supportive actions with other herbs. Saponin chemical constituents from astragalus root (*Astragalus membranceus*) and glycyrrhizic acid from licorice root were studied separately and in combination in rat models of hepatic fibrosis (53). These 2 plants are used in Traditional Chinese Medicine formulas to treat liver disease, among many other things. It was discovered that these constituents work more effectively together to significantly reduce liver hydroxyproline levels, collagen fiber hyperplasia, and serum ALT levels through inhibition of the transforming growth factor beta 1 signaling pathway in hepatic cells.

Licorice root has shown potential hepatoprotective benefits in rats and mice with induced liver disease through its antioxidant and anti-inflammatory actions. In vitro, the active compounds in licorice root extract, glycyrrhizic acid and flavonoid constituents liquiritin and liquiritigenin, inhibited pro-inflammatory mediators iNOS, COX-2, TNF-α, IL-1β, and IL-6. In vivo, licorice extract was shown to inhibit TNF-α, IL-1β, and IL-6 in treated mice (54). In another study, licorice root extract had a protective effect against alcohol-related liver changes in mice by restoring levels of hepatic glutathione, important in antioxidant and detoxification functions of the liver, as well as inhibiting production of TNF-α (55). Additionally, glycyrrhizin was shown to have a hepatoprotective effect against induced obesity and metabolic syndrome in rats through its antioxidant and anti-inflammatory actions (56).

Immune Support

The immune modulatory effects of licorice root have been studied for some time and may indicate a supportive role

in infectious as well as autoimmune and inflammatory conditions. Though the exact mechanism is not yet clear, licorice root extract has been found to modulate the immune response by increasing the induction of regulatory T (Treg) cells in vitro and in vivo (57). The flavonoids isoliquiritigenin and naringenin were identified as active chemical constituents in this action, which may be important in autoimmune and inflammatory conditions. In the same study, oral licorice extract and the 2 isolated constituents all enhanced the immune suppressive action of Treg cells and significantly reduced the clinical severity of experimentally induced inflammatory bowel disease in mice as compared to a control treatment using water. Splenic and lymph node Treg cell levels showed a modest increase, while peripheral blood and colonic cells had a significant increase in Treg cell numbers.

Gastroprotective Effects

In a limited study, healthy beagle dogs were given 2 mg/kg of the NSAID robenacoxib daily for 3 weeks. A second group was given each day, in addition to the NSAID, 50 mg licorice extract and 0.1 ml/kg of an herbal solution consisting of saponariae root (*Saponaria officinalis*), thyme (*Thymus vulgaris*), Icelandic lichen (*Cetraria islandica*), and hyssop root (*Hyssopus officinalis*) (58). A third control group received an empty pill capsule daily. The group given the herbal treatment with NSAID had a significant reduction in ulceration of colonic mucosa compared to the NSAID alone group, determined by endoscopy samples taken initially and at 3 weeks. None of the dogs showed clinical signs of gastrointestinal ulceration.

Cough Support

Compared with codeine (10 mg/kg) as a cough-suppressant in guinea pigs, a water-extracted polysaccharide of licorice root, arabinogalactan (50 mg/kg), had the strongest antitussive effect with an 81% reduction in cough response to an aerosolized citric acid irritant, whereas codeine suppressed coughing 62% of the time (59). Other herbal arabinogalactans tested were from ashwagandha (61% cough suppression) and adhusa (*Adhatoda vasica*) (67% cough suppression). Water served as a negative control. Antitussive effect may be due to topical adhesion and protection from irritation by the polysaccharides, increased moisture and mucous secretion, and the anti-inflammatory, antioxidant, and other effects of the phytochemicals. No adverse effects were seen with the polysaccharides.

Topical Treatment

Topically, licorice root has been used as an anti-inflammatory and antimicrobial treatment, often as a replacement for steroid cream. In a 4 week, prospective, randomized, investigator-blinded, controlled half-side comparison test in human patients with atopic dermatitis, an emollient containing licochalcone A, a constituent of licorice, was used on 1 arm, while a 1% hydrocortisone cream was used to treat the other arm (60). Both sides responded similarly with significant improvement of clinical signs, improvement of skin barrier function, and a reduction of *Staphylococcus aureus* colonization.

In a randomized, double blind, prospective, placebo-controlled trial, licorice root gel was used to treat atopic dermatitis in human patients (61). A 2% formulation showed significant improvement over both 1% gel and placebo based on signs of pruritus, edema, and erythema.

Antimicrobial Effects of Herbs

Herbal therapies are often used against infectious disease with the combined effects of immune support and antimicrobial action. Various herbs have been found to have antibacterial, antiviral, antifungal, antiparasitic, and other antimicrobial benefits. This method of treatment may substitute or work in conjunction with pharmaceutical drugs. The reduction in the need for antibiotic and other pharmacological treatments for infections may help with the increasing problem of microbial antibiotic resistance. The antimicrobial actions of many herbs, including those discussed in this paper, have been demonstrated in vitro and in vivo. Marshmallow root (*Althaea officinalis*), rosemary leaves (*Rosmarinus officinalis*), licorice root (*Glycyrrhiza glabra*), and chamomile flowers (*Chamomilla recutita*), among others, were found to have antimicrobial action against *Escherichia coli* (62). Methanol extracts of marshmallow root (*Althaea officinalis*), arnica flowers (*Arnica montana*), witch hazel leaves (*Hamamelis virginiana*), calendula flowers (*Calendula officinalis*), and lemon balm leaves (*Melissa officinalis*) were all found to be effective against multiple species of periodontal bacteria in vitro, with the first 3

being most effective (63). Anticandidal and antibacterial actions along with cytotoxic and antioxidant activities were demonstrated by *Calendula arvensis* (related to *C. officinalis*) (64).

Conclusion

There is a growing collection of scientific studies striving to determine the mechanisms of action and effects of herbal therapies that have been used traditionally for thousands of years. Some studies are certainly more rigorous than others, and further research is needed to verify and expand upon the findings, but there are some common threads that help to explain the longevity of herbal medicine. All of the herbs discussed here support healing and comfort through anti-inflammatory and antioxidant actions in addition to their individual properties and clinical effects. The 6 herbs investigated here, when used appropriately, represent low toxicity, safe treatment possibilities for a wide spectrum of conditions from inflammation of various causes, musculoskeletal pain, gastrointestinal discomfort, skin wounds, oral disease, cough and respiratory discomfort, anxiety, cognitive decline, decreased function of liver and other organs, infection, and neoplasia. These herbs can be used alone or in conjunction with other therapies to achieve the best possible results for individual patients.

Herbal medicine can be administered in various forms including teas, tinctures, pills, creams, ointments, or as fresh or dried plants. It can be applied topically, mixed in food, syringe-fed, or even given rectally in some instances. Simple formulations can be created through herbal combinations, or plants can be used singly for specific indications. Consultation with a trained veterinary herbalist for prescribing details is recommended to ensure proper herb choice, dosing, quality sourcing, improved palatability, ease of administration, and to avoid undesirable contraindications or herb-drug interactions.

Along with herbal medicine, palliative care can come in many forms including conventional pharmaceutical medications, palliative radiation or surgery, acupuncture or acupressure, chiropractic treatments, massage, physical rehabilitation, essential oils, homeopathy, Reiki, and music therapy. An integrative, multimodal approach can offer a balanced and varied array of options to our patients and their families during the end-of-life journey. The main goal in animal end-of-life care is to provide comfort and to support the best quality of life possible. Judicious use of herbal therapies can offer gentle, effective, palliative medicine in combination with other therapies as indicated in each individual case.

Commentary

I would like to express my sorrow and gratitude for the many lives given by laboratory animals to bring this information to light. May we continue to improve our thinking and research methods to better serve all living beings.

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College of Integrative Veterinary Therapies: excerpt from thesis presented for the Graduate Diploma of Veterinary Western Herbal Medicine

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Endnote

a. Online survey to VBMA (Veterinary Botanical Medicine Association) and CIVT (College of Integrative Veterinary Therapies) members and students 2015; 26 respondents.

References start on page 38.

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