

## Nutraceutical Therapies to Modify Behavior

### WILD WEST VETERINARY CONFERENCE 2017

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#### Introduction

Natural is appealing. Many pet families resist accepting medications as the only option for themselves or their pet; instead seeking nutraceutical and botanical options. Fear and anxiety in pets are often overlooked or misunderstood and, if allowed to continue untreated, the pet may suffer needlessly. Early and appropriate intervention is essential. For major behavior problems, such as severe or extreme manifestations noise related phobias, compulsive disorders, and aggression, medications are appropriate and should not be withheld. People are more aware of their pet's anxiety and more focused on alleviating the pet's distress. Thus, as the awareness of signs and symptoms of mild anxiety is increased, clients will be seeking a variety of options. Previously the dog that was barking was a bad dog. Now we know that dog may be afraid. Clients may ask about nutraceutical options but do you know what to recommend? From new products to old favorites: from research to clinical applications; this presentation provides an overview of natural, non-prescription anxiolytics which may reduce anxiety or fears in dogs and cats.

#### Objectives of the Presentation

The objectives of this presentation are to review common and useful ingredients for alleviation of anxiety and provide the clinician with information about available commercially available nutraceuticals.

#### Nutraceutical and Botanical Defined

Foods, spices and herbs have been used as folk medicine in many cultures for centuries. Hippocrates, father of Western medicine said "**Let food be thy medicine and medicine be thy food**" [431 B.C.]. Botanicals are plants or plant parts used for flavor, fragrance, or medicinal/therapeutic properties. Herbs and spices are two subsets of botanicals. Botanicals may be whole plants, part of a plant or these plants may be further modified by purification or concentration of extracts. The modern nutraceutical market began to develop in Japan during the 1980s. By 1989, the word **nutraceutical**, a portmanteau of the words "nutrition" and "pharmaceutical", was created.<sup>1</sup> Nutraceuticals are products derived from food sources that are purported to provide extra health benefits and the term may be applied to isolated nutrients, dietary supplements, herbal products or specific diets. Terminology varies by region and is determined legally. In the U.S., a botanical may be considered a dietary supplement if it meets specific following definitions according to the 1994 Dietary Supplement Health and Education Act (DSHEA). Many botanicals may meet the criteria for a nutritional supplement. Surveys suggest that more than half of all clients in a veterinary practice are using one or more forms of alternative medicine, either for themselves or their pets and estimates suggest more than 158 million Americans regularly consume dietary supplements. The nutraceutical industry has grown and it is projected that the worldwide nutraceuticals market would reach USD\$250 billion by 2018.<sup>2</sup>

#### Practical Considerations

A quick search on the internet or a stroll down the aisle at the pet store reveals a confusing myriad of botanical products for dogs and cats. They have pretty labels and pictures of happy pets but ingredients that may or may not be effective for the alleviation of pet emotional distress. At best these ingredients may be harmless and ineffective while at the worst case scenario they may disguise ingredients that may have serious risks for adverse effects. Kava Kava is reported to have caused hepatic failure in people and is thus no longer available in some countries. St. John's Wort is similar to fluoxetine, a selective serotonin reuptake inhibitor SSRI. St. John's Wort may cause prolonged bleeding times. Be sure to ask about natural products administered before a surgery or dental when excessive bleeding may be a serious concern. St. John's Wort should not be administered with SSRIs such as fluoxetine, tricyclic antidepressants (TCA) such as clomipramine or monoamine oxidase type B (MAO-B) inhibitors such as selegiline or amitraz. Amitraz may be found in some tick prevention collars. Seems unlikely that someone selecting a natural product would also be giving their pet an SSRI? Situational medications are common adjuncts to SSRIs. Often other pets in the house are anxious as well and clients may reach for a natural product to alleviate the "normal" pet's anxiety. Recently a client of mine gave a large amount of OTC 5-HTP to her dog that was already under treatment with an SSRI. The result (besides me being awoken at 3am by the ER doc): serotonin syndrome. The dog was panting and would not settle down. Physical examination revealed a rapid HR, elevated body temperature and no other determined cause. After a night of nursing care with the emergency department, the dog was fine.

#### Anxiolytics: Nutraceuticals, or Pharmaceuticals?

In many clinical behavior cases, anxiolytics play a pivotal role in the treatment, amelioration or management of the relief of clinical signs associated with fear, stress and anxiety in dogs and cats. Anxiolytics are used in conjunction with protective strategies of avoidance and management of the environment to reduce exposure to the perceived threat while behavioral modification strategies are implemented. Anxiolytics are particularly useful when the occurrence of the primary stimulus cannot be completely controlled (e.g., noises, storms, car rides, grooming, walks, or veterinary visits). Anxiolytics including pharmaceuticals, pheromones, or nutraceutical supplements may reduce fear, stress, anxiety, and their resultant behaviors.<sup>3</sup> Nutraceutical supplements provide a comfortable early intervention option. The goal is not sedation or tranquilization. The goal of an optimal anxiolytic effect is to reduce the anxiety sufficiently to allow natural habituation or create an environment whereby the pet may learn to be less afraid in the face of the fear evoking stimuli. This optimizes daily experiences and allows the owner to direct the learning experience. By reducing the pet's overall fear, anxiety and distress, anxiolytics "open the door" to allow for successful learning during implementation of a behavior modification program.

## Veterinary Herbs, Supplements, and Nutraceuticals

**Alpha-casozepine** ( $\alpha$ -S1 tryptic casein) is a tryptic hydrolysate of  $\alpha$ -S1 casein, a protein found in cow's milk. It is similar in structure to gamma amino butyric acid (GABA) which likely explains its affinity for GABA-A receptors producing an effect similar to many benzodiazepines. Alpha-Casozepine is used to treat fear, anxiety, stress, and related behavior problems. There are no known or reported side effects or contraindications. Zylkene® is highly palatable and be administered by putting the contents of the capsule on dry or canned food. It is labeled for both dogs and cats. In one study in dogs, it was determined to be equally effective as selegiline in reducing anxiety in dogs based on owner assessment and EDAD (Emotional disorders and evaluations in dogs) score. Selegiline is approved for emotional disorders in many countries in Europe and, in this study, alpha-casozepine was considered equally efficient and successful in reducing the EDAD score and correlated to owner assessments.<sup>4</sup> In a placebo controlled study in cats, it significantly improved fear of strangers, contact with familiars, general fear, fear related aggression and autonomic signs.

**Alpha-lactalbumin** is a unique protein component of milk which is obtained by purified extract from milk whey protein. Whey is the "watery" by product of cheese production that separates from the curds when making cheese. Concentrated whey milk protein provides many proteins and benefits but the most notable of the ingredients in the extract is alpha-lactalbumin. Concentrated whey protein contains 10 essential amino acids including the essential amino acid, L-tryptophan, a precursor of the neurotransmitter serotonin, and cysteine which is an important antioxidant. Cysteine may increase endogenous production of glutathione, the master antioxidant. Brain serotonin levels increase under stress since the neurotransmitter is important in regulating emotional states and moods. Chronic stress and anxiety may lead to a depletion of available concentrations of serotonin and tryptophan, causing serotonin levels to fall below functional needs.<sup>5</sup> Alpha-lactalbumin, contains a high tryptophan content (approx. 4%) compared to other food protein sources, and studies suggest that dietary supplementation of alpha-lactalbumin improves cognitive performance in stress-vulnerable subjects via increased brain tryptophan and serotonin activities.<sup>5</sup>

**Docosahexaenoic acid (DHA).** Omega-3 fatty acids, especially docosahexaenoic acid (DHA), play important roles in development of vision and the central nervous system, maintaining neuronal integrity and enhancing energy use by neurons. DHA may also improve early learning in people and animals. The primary source of DHA is milk from your puppy's mother and may be included in puppy diets (such as Hill's® Science Diet® Puppy). Polyunsaturated fatty acids are used to facilitate healthy brain and retinal development and learning in young animals, to improve cognitive abilities in senior pets, and help to manage issues of fear and anxiety. Cats may lack the liver capacity to synthesize longer-chain omega-3 and omega-6 fatty acids. High doses of polyunsaturated fatty acids should be avoided due to the potential for gastrointestinal effects, altered immune function, altered platelet function, and weight gain.

**L-theanine** is a structural analogue of the amino acid glutamate, the most important excitatory neurotransmitter of the nervous system. Theanine, found naturally in black, green and white tea, is thought to exert neuro-protective effects by binding and blocking glutamate receptors, thus reducing excitatory impulses and lowering the stimulatory effects of glutamate.<sup>6,7</sup> Animal studies also suggest that theanine increases the levels of stabilizing neurotransmitters such as serotonin, dopamine, and  $\gamma$ -aminobutyric acid (GABA) in the brain. Theanine also directly stimulates the production of alpha brain waves, which create a state of deep relaxation, daytime wakefulness, and mental alertness which supports a once a day, morning dosing regimen.<sup>6,7</sup> Theanine is uniquely palatable. The effects of theanine have been evaluated in dogs and cats and indicate that theanine may reduce signs of anxiety in cases of fear of humans,<sup>8</sup> noise phobias, travel anxiety, and urine marking.

**Melatonin** is a hormone and an indoleamine derivative of serotonin may inhibit dopamine. It is naturally synthesized from serotonin in the pineal gland which is secreted at high levels during the night and low levels during daytime. Melatonin has an impact on sleep-wake cycle. It appears to influence the circadian rhythm information transmitted from the suprachiasmatic nucleus to the hypothalamus.

Physiologic mode of action of melatonin has not been fully elucidated in humans; it may decrease free radical production, reduce central nervous system excitability and potentiate GABA. Side effects in people include sleepiness, headaches or gastrointestinal discomfort. Generally appears to be benign in dogs though potency and effect for behavior may be difficult to assess. Melatonin is often useful for treatment of certain dermatologic conditions. Behaviorally, melatonin has been reported to be useful in easing noise-related fears or phobias and nighttime waking in dogs.

**Magnolia officinalis** extracts have long been utilized in polyherbal combinations in traditional Chinese and Japanese herbal medicine. Magnolia extracts, most specifically the constituent's honokiol and magnolol, enhance the activity of both synaptic and extra-synaptic GABA receptors in the brain. GABA is the brain's chief inhibitory neurotransmitter which modulates the activity of overexcited neurons stimulated by fear and anxiety. The action of these compounds is thought to be selective binding to specific GABA-benzodiazepine receptors which may explain why the effects of honokiol and magnolol are similar to diazepam, without the sedative effects.

**Nepeta cataria (catnip or catmint).** Catnip exerts its influence on the CNS through the olfactory bulb, but not the vomeronasal organ. The active ingredient in catnip, *Nepeta cataria*, is the essential oil nepetalactone, which is a terpene composed of two isoprene units with a total of 10 carbons. Catnip or catmint produces an apparent euphoric or hallucinogenic reaction in about 50% to 75% of cats, and responsiveness is reported to be an autosomal dominant trait which may be noted beginning at about 8 weeks of age. Affected cats may exhibit a range of behaviors, including sniffing, licking, and chewing the plant, head shaking, chin and cheek rubbing, head rolling, and body rubbing. This reaction lasts for 5 to 15 minutes and then may be initiated again for another hour or more. Catnip is available as a leaf, but liquid and aerosol forms are also available. Volatile oils appear to exert a cholinergic effect, which may account for some of their psychoactive properties. Catnip may be useful for enrichment, reinforcement-based training, response substitution, and counterconditioning. Generally considered safe and non-addictive, there is one case of catnip intoxication which has been reported.

**Phellodendron amurense** is a species of tree commonly called the Amur or Chinese Cork tree, and the major source of huáng bǎi, one of the fundamental herbs of Chinese medicine. *Phellodendron* extracts are rich in berberine, which has demonstrated similar anxiolytic effects as diazepam and buspirone in experimental anxiety models in mice, though the exact mechanism is still unknown. Though the name sounds similar, *Phellodendron amurense* is not the same as the toxic

ornamental houseplant *Philodendron*. The combination of *Magnolia* plus *Phellodendron* extracts appears to be synergistic, with the combination controlling stress and anxiety more effectively than either compound used alone. In a laboratory model, the combination of *Magnolia* and *Phellodendron* (*Harmonease*<sup>TM</sup>) reduced anxiety in beagles in a placebo-controlled clinical trial of noise-induced anxiety.<sup>9</sup>

**S-adenosyl-L-methionine (SAME)** is a chemical found in all living cells which is formed from methionine and ATP. SAME donates methyl groups to a variety of compounds such as phospholipids, proteins, and nucleoproteins. SAME may help to maintain cell membrane fluidity, receptor function, and the turnover of monoamine transmitters, as well as increase the production of glutathione. In people it is considered an antidepressant drug in some countries and in others it is considered a supplement for depression but in veterinary medicine these mood elevating benefits remain unexplored at this time. SAME may be beneficial to augment SSRIs and TCAs but should be administered with monitoring by a veterinarian or behaviorist.

SAME may help to maintain cell membrane fluidity, receptor function, and the turnover of monoamine transmitters, as well as increase the production of glutathione. In a placebo-controlled trial in dogs, greater improvement in activity and awareness was reported in the SAME group after 8 weeks. SAME is available in canine formulations for cognitive decline and hepatic dysfunction: Novifit® by Virbac and both Denosyl® and Denamarin® (a combination of SAME and Silybin) by Nutramax Laboratories. S-adenosyl-L-methionine (SAME) is considered to be safe with few reported side effects; however, SAME is relatively expensive and unstable so the manufacturing and handling processes are extremely important; the quality of product may vary and impact clinical efficacy.

**Souroubea proprietary blend.** Zentrol® (VPL, Phoenix, AZ) is a non-sedating, non-pharmaceutical formulation for natural stress management and alleviation of undesirable behaviors in dogs associated with boarding, traveling, separation anxiety, and other circumstances. The tablets are composed of natural ingredients, *Souroubea* spp, containing betulinic acid, and *Platanus* spp, which are shown to help reduce stress related behaviors and lower cortisol levels. Comes in a 60-count bottle. Chewable 500-mg tablets are dosed once daily.

**Tryptophan.** Though tryptophan (TRP) is a known precursor to serotonin and an essential amino acid, the behavioral benefits of supplementation of tryptophan is still considered controversial and widely debated. The aromatic amino acids tryptophan, tyrosine and phenylalanine are precursors to the neurotransmitters serotonin, dopamine and norepinephrine and while these amino acids are necessary for synthesis of these neurotransmitters. The pathway from dietary ingestion to the neurocellular level is complicated by digestion, bioavailability, serum protein binding, and crossing of the blood brain barrier (BBB) bound by carrier amino acids. Tryptophan is highly bound to albumin. Serotonin (5HT) is synthesized from tryptophan in brain neurons so it is dependent upon blood and brain Trp levels. Transport of tryptophan is mediated by a competitive transporter system shared by large neutral amino acids (LNAA). Transport of tryptophan by the brain neurons is influenced by the relative concentration of amino acids; presence of alpha lactalbumin may result in an increase in the plasma ratio of tryptophan to other LNAA. Whey protein concentrates which contain both alpha lactalbumin and tryptophan should yield a greater impact on synthesis on serotonin within brain cells than sources which contain only isolates of tryptophan.<sup>5</sup>

Protein levels and protein proportions in the diet may have an impact on relative availability of tryptophan for transport across the BBB. In one study of dogs displaying dominance aggression, territorial aggression or hyperactivity, tryptophan supplementation was hypothesized to be beneficial. Subjects were given either a low protein diet or a high diets and then supplemented with L-tryptophan (L-Trp). The dogs on a low protein diet + LTRP were shown to lower owner reported behavior/aggression scores in dogs diagnosed as territorial or dominance aggression while high protein diets without tryptophan were associated with greater aggression.<sup>10</sup>

While tryptophan is widely available as an OTC supplement its effects may not be beneficial and may not be without risks. While augmentation of an SSRI or TCA by addition of dietary source of tryptophan may help to insure adequate serotonin levels, there is risk for serotonin syndrome, particularly when combined with these serotonin enhancing medications. Signs of serotonin syndrome include agitation, trembling, pacing, shaking, hyperthermia, tachycardia, diarrhea, twitching, tremors, seizure and (rarely) death. Eosinophilia-myalgia syndrome has been reported people. Pancreatic atrophy has been reported with tryptophan supplementation. Tryptophan is a potent stimulant of pancreatic synthesis in dogs. After absorbing L-tryptophan from food, the body converts it to 5-HTP (5-hydroxytryptophan). There are OTC formulations of 5-hydroxy-L-tryptophan (5HTP). However, 5HTP readily crosses the blood brain barrier and is rapidly converted to serotonin within 1 to 2 hours of absorption so there is a risk of serotonin syndrome. Gastrointestinal and neurological signs consistent with serotonin syndrome have been reported in dogs. L-Tryptophan is a common component of nutraceutical formulations intended to alleviate anxiety and pets and in people with frequent enthusiastic anecdotal reports of effectiveness.

**Other herbals, supplements, and nutraceuticals.** Currently there is not research, efficacy or reputable veterinary formulations for many other available botanicals including *Hypericum perforatum* (St. John's Wort), *Eleutherococcus* (Siberian ginseng), *Passiflora incarnate* extract (Passionflower), *Scutellaria laterifolia* and *S. baicalensis* (Skullcap), hops, *Valeria officinalis* (Valerian) and kava kava.

Key ingredients and examples of veterinary formulations

Ingredient	Classification	Examples of veterinary formulations which include each ingredient <sup>1,2</sup>
Alpha-casozepine	Nutraceutical	Zylkene® (Vetoquinol), Royal Canin® CALM diet
Alpha-lactalbumin	Nutraceutical	Solliquin <sup>TM</sup> (Nutramax)
Docosahexaenoic acid (DHA)	Fatty acid	Hill's® Science Diet® Puppy
L-theanine or sun theanine®	Nutraceutical	Anxitane® (Virbac), Solliquin <sup>TM</sup> (Nutramax), Composure <sup>TM</sup> PRO (Vetriscience), GNC® Pets Ultra Mega Calming, Calmex® (VetPlus)

Melatonin	Hormone	None
<i>Nepeta cataria</i> , Catnip	Herbal	None
<i>Magnolia officinalis</i>	Herbal	Solliquin™, Hormonease® (VPL)
<i>Phellodendron amurense</i>	Herbal	Solliquin™, Hormonease®
S-adenosyl-L-methionine (SAME)	Nutraceutical	Denosyl®, Denamarin® (Nutramax), NOVIFIT® (NoviSAMe®) Tablets (Virbac)
<i>Souroubea</i> spp & <i>Platanus</i> spp	Nutraceutical	Zentrol (VPL)
L-Tryptophan	Nutraceutical	Pro-Quiet, Composure™ PRO, Royal Canin® CALM, Calmex® (VetPlus)

1. Examples are listed to be representative and biased by author familiarity. The number of available products is rapidly increasing and products on the market may change.

2. See package labels for dosing guidelines. Most doses for natural products are derived from human dosing recommendations and may be limited by toxicity findings in rodent studies. Few dose controlled clinical trials are done to determine the doses listed above.

#### Regulation, Self-Regulation, and Veterinary Specialization

A commonly expressed concern is for lack of standardization between similar sounding products and even variations within batches. Adverse effects, toxicity and contraindications have yet to be established for many nutraceuticals and botanicals and there are very few efficacy studies.

The purity, consistency and efficacy of natural products may vary widely so when selecting nutraceutical products the consumer should focus on familiar and reputable companies. Be sure the manufacture is compliant with Good Manufacturing Practices (GMP) with strict Quality Control to verify all ingredients meet product specifications and Quality Assurance to confirm the product meets label claims. Manufacturers of supplements in North America may participate in voluntary self-regulation and by organizations such as: the Nutraceutical Alliance ([www.nutraceuticalalliance.com](http://www.nutraceuticalalliance.com)) based in Canada, and the National Animal Supplement Council (NASC; [www.nasc.cc](http://www.nasc.cc)), based in the USA. Consumers should be advised to select and support companies who have proven a dedication to quality control and production of consistent products.

The Veterinary Botanical Medicine Association" is a group of veterinarians and herbalists dedicated to developing responsible herbal practice by encouraging research and education, strengthening industry relations, keeping herbal tradition alive as a valid information source, and increasing professional acceptance of herbal medicine for animals." There is even a new specialty: The American College of Veterinary Botanical Medicine was established in 2014 to increase the proficiency and competence of veterinarians in the use of medicinal plants, ultimately leading to diplomate status in the specialty of veterinary botanical medicine.

The use of alternative and complementary treatments has increased in human and veterinary medicine. Although there is still much work to be done regarding many modalities, there is a growing body of literature that suggests there may be biological effects which may result in clinical improvement. However, additional research is necessary to determine appropriate use, dose considerations, and degree of efficacy.

#### Resources

- Veterinary Botanical Medicine Association (VBMA) [www.vbma.org](http://www.vbma.org) (<http://www.vbma.org>)
- American College of Veterinary Botanical Medicine (ACVBM) [www.acvbm.org/index.html](http://www.acvbm.org/index.html) (<http://www.acvbm.org/index.html>)
- American Holistic Veterinary Medical Foundation (AHVM) [www.ahvmf.org](http://www.ahvmf.org) (<http://www.ahvmf.org>)
- American College of Veterinary Behaviorists (ACVB): [www.dacvb.org](http://www.dacvb.org) (<http://www.dacvb.org>)
- American Veterinary Society of Animal Behavior (AVSAB): [www.avsabonline.org](http://www.avsabonline.org) (VIN editor: URL is not accessible as of 9/17/2017.)
- The Society of Veterinary Behavior Technicians (SVBT): [www.svbt.org](http://www.svbt.org) (<http://www.svbt.org>)

#### References

1. Kalra EK (2003). Nutraceutical-definition and introduction (PDF). *AAPS pharmSci*. 2003;5(3):27–28. doi:10.1208/ps050325. PMC 2750935. PMID 14621960.
2. Staff, Global Industry Analysts, Inc. July 1, 2012 Market Research Report: Nutraceuticals.
3. Landsberg G, Hunthausen W, Ackerman, L. Complementary and alternative therapy for behavior problems. In: Behavior problems of the dog and cat. 3rd ed. Oxford, UK: Saunders; 2013:139–149.
4. Beata C, Beaumont-Graff E, Diaz C, et al. Comparison of the effect of alpha-casozepine (Zylkene) versus selegiline hydrochloride on anxiety disorders in dogs. *J Vet Behav*. 2007;2:175–183
5. Fernstrom JD et al. Large neutral amino acids: dietary effects on brain neurochemistry and function. *Clin Nutr*. 2013;32:1073–1076.
6. Nobre AC, Rao A, Owen GN. L-theanine, a natural constituent in tea, and its effect on mental state. *Asia Pacific Journal of Clinical Nutrition*. 2008;17:167–168.
7. Nathan PJ, Lu K, Gray M, Oliver C. The neuropharmacology of L-theanine (N-ethyl-L-glutamine): a possible neuroprotective and cognitive enhancing agent. *J Herb Pharmacother*. 2006;6:21–30. doi:10.1300/J157v06n02.
8. Araujo JA, de Rivera C, Ethier JL, et al. ANXITANE tablets reduce fear of human beings in a laboratory model of anxiety-related disorders. *J Vet Behav*. 2010;5:268–275.
9. DePorter TL, Landsberg GM, Araujo JA, et al. Hormonease chewable tablets reduces noise-induced fear and anxiety in a laboratory canine thunderstorm simulation: a blinded and placebo-controlled study. *J Vet Behav: Clin Appl Res*. 2012;7:225–232.
10. De Napoli JS et al. Effect of dietary protein content and tryptophan supplementation on dominance aggression, territorial aggression and hyperactivity in dogs. *J Am Vet Med Assoc*. 2000;217(4):504–508.

#### SPEAKER INFORMATION

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