# Functional Foods and Nutraceuticals: What's Up in 2016?

**Susan G. Wynn, DVM**
BluePearl Georgia Veterinary Specialists
Nutrition and Integrative Medicine
Sandy Springs, GA
wynndvm@gmail.com

## Abstract

With the advent of populist medicine (thanks to the alternative medicine movement and the Internet), the order in which new dietary therapies become widespread has reversed from doctor to patient and now consumer to medical advisor. In some cases, consumer use and demand predated medical research that ultimately showed clinical benefits. Probiotics are one example, now having the largest supplement sales in commerce. In other cases, clinical benefits have not been shown in studies or practice despite early popularity, such as occurred with CoEnzyme Q10 and glandular extracts. Nutritionists should be aware of the use and present understanding for a few of the more popular alternative dietary supplements. Regulation and quality control continue to challenge the industry, which claims to be formulating a plan.

**Glossary of Abbreviations**
**CBC:** Cannabinol
**CBD:** Cannabidiol
**CBDA:** Cannbidiolic Acid
**CBG:** Cannabigerol
**GAPS:** Gut and Psychology Syndrome
**GERD:** Gastroesophageal Reflux Disease
**PBL:** Peripheral Blood Lymphocytes
**PSK:** Polysaccharide-K
**PSP:** Polysaccharide Peptide
**PTSD:** Post-Traumatic Stress Disorder
**PUFA:** Polyunsaturated Fatty Acids
**RCT:** Randomized Controlled Trial
**THC:** Δ-9-Tetrahydrocannabinol
**THCA:** Δ-9-Tetrahydrocannabinol Acid

## Introduction

According to *Nutraceuticals World* magazine, probiotics are the most successful functional ingredient in packaged foods after vitamins and minerals. Probiotic sales increased 22% last year, making them the fastest-growing category of functional food.

First, some definitions. A functional food is a revised food that claims to improve health by providing benefit beyond that of the traditional nutrients it contains. Functional foods include items such as cereals, breads and beverages that are fortified with vitamins, herbs, nutraceuticals, and bone broth as mentioned below. A nutraceutical is a fortified food or dietary supplement that provides health benefits in addition to its basic *nutritional* value (Merriam-Webster). A botanical or medicinal herb consists of whole or extracted plants.

Veterinarians in integrative practice report that some of the most recent popular nutraceuticals include:

1. Golden Paste
2. Bone Broth
3. 1-Tetradecanol Complex (1-TDC)
4. Medicinal Mushrooms
5. Cannabis
6. Apple Cider Vinegar
7. Coconut Oil

### Golden Paste

Consisting primarily of turmeric, golden paste is touted as an antioxidant and anti-inflammatory used chiefly for osteoarthritis and to prevent and treat cancer. In people, turmeric has been used principally for the treatment of patients with acid, flatulent or atonic dyspepsia (German Commission E, 1985). It also is used to prevent cardiovascular disease, asthma and eczema and to improve the function of the gastrointestinal tract. Turmeric extracts are used as an antioxidant for the treatment of hepatic disease. In laboratory animal studies, turmeric extracts protect the liver against inflammation caused by galactosamine, lipopolysaccharide, diethylnitrosamine, and carbon tetrachloride.

The potential clinical benefits of curcumin found in turmeric have been widely studied. A PubMed search on the word "curcumin" produces over 8,400 citations. There are other active components within the turmeric rhizome. Curcumin-free turmeric components possess numerous biological activities including anti-inflammatory, anticancer and antidiabetic activities.[1] Some of the major compounds of turmeric oil include aromatic (ar)-turmerone (28%), turmerone (17%), turmerone, curlone (14%), 2-carene (5%), zingiberene (4.37%), sesquiphellandrene (6%), ar-curcumene (3%), and linoleic acid (5%).[1]

Multiple clinical trials in people have shown benefit for inflammmation and pain associated with osteoarthritis.[2] A curcumin compound administered as an adjunct to chemotherapy in 80 people with solid tumors resulted in a significant

From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.

improvement in quality of life and suppressed systemic inflammation.[3] Curcumin supplementation decreased proteinuria in patients with diabetic and lupus-associated nephritis.[4,5] Curcumin has low oral bioavailability, and most recent trials make use of lipid-enhanced forms of the compound to increase absorption. However, turmeric and curcumin may undergo metabolism that increases bioavailability of active compounds.[6]

Possible adverse effects of turmeric have been published, but reports of actual toxicity have been rare. It isn't recommended for use during pregnancy as it may stimulate uterine contractions. Other potential (but undocumented) adverse effects include:

- Gallbladder Problems: Traditionally known as a cholagogue, tumeric should not be used if bile duct obstruction is suspected or possible.
- Surgical Patients: Turmeric may have anticoagulant activity, so caution is advised in people who will undergo surgery.
- Diabetes: Curcumin may decrease blood glucose, so interactions with diet changes, insulin and hypoglycemic drugs should be kept in mind.
- Gastroesophageal Reflux Disease (GERD): Turmeric causes gastric upset in some people, so it is said to be contraindicated in people with GERD.
- Hormone Sensitive Tumors: Curcumin may have estrogenic activity, thus there is some caution not to use it in patients with hormone-sensitive tumors. Other authors suggest a possible benefit.
- Fertility Treatments: Turmeric is said to be contraindicated in people undergoing fertility treatments, so it may lower testosterone levels and decrease sperm motility.
- Iron Absorption Problems: Turmeric, in large amounts, may inhibit iron absorption.

Golden paste is often recommended for dogs with osteoarthritis, cancer and chronic inflammatory conditions. The usual recipe for golden paste consists of ½ cup powdered turmeric, 1 cup water, ¼ cup coconut oil, and 1 ½ teaspoon black pepper, gently heated. The usual dose for dogs is ¼ teaspoon to 1 tablespoon, divided daily.

In people, the dose of curcumin used in published studies is as high as 6 grams per day. The published dose of turmeric for dogs and cats is:

- Curcumin: canine, 50-250mg TID; feline, 50-100mg QD
- Dried herb: 50-600mg/kg, divided daily (optimally, TID) (to maximum palatability tolerance)

**Bone Broth**

Bone broth is an increasingly popular component of the paleo diet and has recently been recommended as a treatment for gut and psychology syndrome (GAPS) including autism, ADHD, depression, and schizophrenia.[7] Advocates claim (as reported on the "Today" show) that bone broth contains "vitamins and minerals from the broken-down bones that have powerful healing properties, and can help to alleviate joint and gut pain, boost your immune system (*http://www.today.com/food/i-tried-bone-broth-week-here-s-what-happened-t75226*), brighten skin, and even make your hair shiny."[8]

There is no single recipe for "healing" bone broth. Cooking may vary from 5 to 24 hours, which will change the nutrient profile. Minerals reach their maximum concentration within 1 to 2 hours, but nitrogen loss is linear over about 7 hours.[8]

Simmering leads to loss of nitrogen and potassium from bones to the water. Loss of iron, calcium and magnesium were greater from soaking in cold water. Inclusion of vegetables, when cooked, increased nitrogen, potassium, iron, calcium, and magnesium in the final product. Other minerals found in the broth are phosphorus, copper, sodium, and chloride. Additional components of bone broth include gelatin and fat. No tyrosine, tryptophan or sulfur were found in the broth.

Although bone broth may provide a bioavailable source of minerals and nitrogen, whether this provides benefit to pets eating complete and balanced diets is questionable.

*Toxicity:*

*Lead*

Bone broth made by boiling chicken carcass contained 7 - 9.5 µg/L of lead, as compared with that of tap water at 0.89 µg/L.[9]

*Hypercalcemia:*

A single case report[10] described a cricket player who drank 1 to 2 liters of bone broth at least 3 days/week for 6 months before developing hypercalcemia. No vitamin D-containing supplements were being taken, and other causes of hypercalcemia were ruled out. The authors presumed that excess vitamin D was coming from bone marrow, as vitamin D is stored in fat; however, no analysis of the patient's soup preparations was reported.[10]

**1-TDC**

The company that produces 1-TDC (1-tetradecanol complex) claims that "1-TDC® Dual Action is a new generation of fatty acid oils with a different molecular structure and properties that are far superior to traditional essential oils."

1-TDC (novel monounsaturated fatty acid mixture, also known as myristyl alcohol and tetradecyl alcohol) is taking the agility world by storm. These fatty acids have been proposed to reduce inflammation via reduced LTB4, IL1, expression of proteoglycan-degrading enzymes, and adhesion molecule expression. The cited references are for a human clinical trial using topical "cetylated fatty acid cream."[11-14] and the supporting trial in dogs is unpublished and poorly reported.

**Medicinal Mushrooms**

Medicinal mushrooms are fungi that have a significant role in traditional Oriental medicine systems, and over 100



From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.

species are found in modern Chinese pharmacopeias. Their use dates back at least to Neolithic times. Fungi are members of neither the plant nor animal kingdoms, and there are an estimated 3 to 5 million species and only a fraction of these have been described. At the current rate of discovery (1,200 new species per year), it will take more than 4,000 years to describe the world's fungal diversity. Fungi have served as a source of compounds such as penicillin, statins, mycophenolate, cyclosporine, and avermectin. There have been over 400 clinical trials and more than 50,000 scientific papers on medicinal mushrooms and their influence on various diseases.

Mushrooms contain relatively high concentrations of carbohydrate, fiber and protein (19 to 35%), including all amino acids essential to humans.[15] The most well-characterized active constituents are polysaccharides, especially β-glucans, which have been shown to activate immune cells and cytokine responses. Human clinical trials have shown that these polysaccharides also attack malignant cells.

Heteropolysaccharides are more complex molecules and have also been shown to exhibit immunomodulatory, antinociceptive and anti-inflammatory activity. Mushrooms also produce pharmacologically active proteins, such as lectins (carbohydrate-binding proteins) that exhibit antiproliferative, proapoptotic and cytotoxic effects. Terpenoids are another active class, with *Ganoderma lucidum* alone containing approximately 150 different triterpenes with different biological activities.[16]

Bioactive components of mushrooms:

- Lectins
- Polysaccharides
- Phenolics
- Polyphenolics
- Terpenoids
- Ergosterols
- Volatile Organic Compounds

Mushrooms and their extracts are used as adjuncts to chemotherapy and radiation in Russia, Japan, Korea, and China. However, the use of whole herbs and complex extracts is difficult to reconcile with medical research and pharmaceutical therapy in the West. Although some research has focused on small molecular weight compounds, the larger polysaccharides cannot be synthesized, limiting large-scale production of any compounds identified as successful therapies.

Proposed Activities of Medicinal Mushrooms

| | |
|---|---|
| Anti-Tumor | Anti-Inflammatory |
| Immunodulation | Detoxification |
| Antioxidant | Hepatoprotective |
| Cardiovascular | Antidiabetic |
| Anti-Hypercholesterolemic | Herbicidal |
| Antiviral, Antiphytoviral | Nematocidal |
| Antibacterial | Anti-Allergic |
| Antiparasitic | Antinociceptive |
| Antifungal | |

The best-studied medicinal uses for mushrooms include:

- Prevention and treatment of immune deficiency/immunosuppression
- Support of patients undergoing radiation and chemotherapy
- Cancer (prevention of oncogenesis, direct anti-tumor activity, metastasis)
- Bloodborne viral infections, especially hepatitis B, C, D
- HIV, HSV, EBV
- Chronic gastritis
- Gastric ulcers due to *Helicobacter pylori*
- Dementia and Alzheimer's disease

Human clinical trials testing β-d-glucans alone and linked with proteins have shown immunopotentiating activity. Species showing cancer inhibitory effects include shiitake (*Lentinus edodes*), maitake (*Grifola frondosa*), Reishi (*Ganoderma lucidum*), Turkeytail (*Trametes versicolor*), Cordyceps (*Cordyceps sinensis*), Royal Sun Agaricus (*Agaricus brasiliensis*), Tremella (*Tremella mesenterica*), and others. Some of the β-glucans shown to have anti-cancer activity include Krestin PSK (polysaccharide-K) and PSP (polysaccharide peptide as in I'm Yunity™) from *Trametes versicolor*, lentinan from shiitake mushrooms, and D fraction from maitake mushrooms.

Most human clinical trials are small and originate from Asian countries. Two meta-analyses, one covering eight randomized control trials (RCTs) including 8,009 human patients and the other analyzing 650 people with gastric cancer, indicated improved survival when mushroom extracts (lentinan from shiitake or PSK from Trametes versicolor) were used as adjunct therapies. A Cochrane review examined 257 trials involving *Ganoderma lucidum* extract, five of which were high quality enough to evaluate 373 patients, mostly with lung cancer, finding quality of life improvements along with enhanced lymphocyte proliferation when patients were treated with the mushroom in addition to conventional therapies.[17] The following mushroom compounds have passed Phase I, II and III clinical trials: schizophyllan, lentinan, polysaccharide K, and Grifon D.

Mushrooms are said to have both immune-stimulant and anti-inflammatory effects. This apparent contraindication likely stems from the usual discrepancies between *in vitro* and *in vivo* studies. *In vitro* studies indicate increased production of proinflammatory cytokines because the cells are affected by all substances in the mushroom extracts and in particular the high molecular weight β-glucans. In human and other *in vivo* studies, lower molecular weight substances are readily absorbed and account for systemic anti-inflammatory effects.[18] The most prominent group of anti-inflammatory compounds are the terpenoids, but activity also has been documented from peptides, steroids, and aromatic and phenolic compounds.

As of this writing, the PSK (polysaccharide-K) extract of turkey tail (*Trametes versicolor*) has undergone more human clinical trials than other compounds. Cancer patients were found to have increased survival, decreased recurrences,

increased disease-free intervals, increased peripheral NK cell activity, increased PBL (peripheral blood lymphocytes) cytotoxicity, IgG, IgM, increased body fat, and decreased patient withdrawal due to disease progression.[19] I'm Yunity™ is a PSP extract of turkey tail that was found to potentially increase survival in dogs with naturally occurring hemangiosarcoma.[20]

Mushroom supplements appear to be safe; severe side effects have rarely been reported from case reports or clinical trials. Shiitake dermatitis, however, is a recognized allergic reaction that occurs rarely.

Uncertainties in medicinal mushroom use include:

1. There are so many species of mushroom that it is critical to confirm that a supplier is using the correct one.
2. Unknown dosing questions as there only are confirmed doses for simple extracts, such as lentinan. There is research showing that high doses lead to immunosuppression.
3. Natural variations exist in bioactive content.
4. Lack of consistent production standards results in many not being cultivable in practical or profitable amounts.

**Cannabis**

Findings in archeological sites suggest that cannabis was in use — even cultivated — for 10,000 years. Neolithic people used the plant for fiber, food, medicine, and ritual. Hemp and marijuana are two cultivars of the species *Cannabis sativa L*. Hemp is nonpsychotropic and contains primarily cannabidiol (CBD), and marijuana is psychotropic and contains higher levels of ð-9-tetrahydrocannabinol (THC). Both cultivars are comprised of many strains with varying phytochemical profiles.

Cannabis contains more than 480 unique compounds, including 85 cannabinoids in addition to terpenoids and noncannabinoid phenols. Cannabinoids are a group of 21-carbon-containing terpenophenolic compounds (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=422394&version=Patient&language=English*). THC is the most important psychotropic compound, and CBD has no psychoactive properties. Recently, other plant species have been found to contain phytocannabinoids including those in the flax (*Linaceae*) and daisy (*Asteraceae*) families.[21]

The endocannabinoid anandamide (from the Sanskrit for "bliss") was discovered in 1992 as a natural cannabinoid receptor agonist, and the endocannabinoid system subsequently was described. Anandamide has similar effects as THC. At least five endogenous endocannabinoids have been described, which function in memory, balance, neuroprotection, and immune function. The endocannabinoid system is a complex lipid-signaling network that modulates nervous system activity, and its effects can be summarized as "relax, eat, sleep, forget, and protect."

The endocannabinoid system is present in all vertebrate systems and is, therefore, thought to have existed for over 500 million years, evolving along with the plants that produce cannabinoids. THC binds cannabinoid receptors, and CBD is an indirect agonist and modulator of THC activity, inhibiting CYP3A,[11] which would otherwise metabolize THC to much more potent psychoactive compounds.

Endocannabinoids are synthesized by postsynaptic neurons and apparently influence presynaptic neurotransmitter release. There are thought to be 13 or more cannabinoid receptors.[21] Anandamide and THC bind the CB1 receptor that is the most abundant G protein-coupled receptor expressed in the human brain. CB1 receptors are found in the brain, myocardium, adipose tissue, vascular endothelium, GI and reproductive tracts, and sympathetic nerve terminals, and are located in highest concentrations near synapses of neurons that release GABA. CB1 receptors stimulate the dopaminergic reward pathway, which motivates eating and substance abuse. They are thought to be related to central and peripheral regulation of food intake, fat accumulation, and lipid and glucose metabolism.

CB2 receptors are found in peripheral macrophages, lymphocytes, natural killer cells, and microglia in multiple areas of the immune and peripheral nervous systems. CB2 receptors are upregulated in the early stages of inflammation in the CNS and peripheral tissues. Other CB receptors are distributed among different cell and tissue types. These receptors are bound by endogenous cannabinoids, plant cannabinoids and synthetic cannabinoids.

Endocannabinoids are long-chain polyunsaturated fatty acids (PUFA) formed from cell membrane omega-6 (n-6) fatty acids with varying degrees of selectivity for cannabinoid receptors. They affect appetite and impair cognition, time perception and short-term memory; they also lead to discoordination, sleepiness and enhanced body awareness. Endocannabinoids affect glucose and lipid metabolism along with fat accumulation and are thought to have a role in insulin resistance and metabolic syndrome.

The main role for endocannabinoids is cell signaling, and as neurotransmitters, they are unique in that they are lipids and hydrophobic. This confers local paracrine (cell-cell) and autocrine (same-cell) activity as opposed to systemic activity. These cannabinoids are formed on demand, have a short half-life, and are not stored. Nonreceptor dependent actions are mediated through many pathways and receptors, including COX-2 and LOX cascades; PPAR, 5-HT1A and 2A, benzodiazepine, glycine alpha1, and alpha1 beta receptors; and TRP channel activation and calcium modulation.

*Potential Clinical Uses for Cannabis*[23]

*Cancer*

Preclinical studies suggest that phytocannabinoids have anticancer properties. CB1 and CB2 receptors have been identified in many tumor types, and malignant tissues tend to express higher numbers of cannabinoid receptors than nonmalignant tissues. Studies suggest that cannabinoid binding of these receptors can lead to cancer cell death



From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.

| Major and Minor Cannabinoids [21,22] | |
|---|---|
| Δ-9-Tetrahydrocannabinol (THC) | Euphoriant, analgesic, anti-inflammatory, antiemetic, antioxidant, bronchodilator, improves symptoms of Alzheimer's disease and duodenal ulcers, muscle relaxant, antipruritic, and is a cholagogue. |
| Δ-9-tetrahydrocannabinolic Acid (THCA) | Predominant cannabinoid in psychoactive strains of cannabis, THCA is nonpsychotropic until activated by smoking or cooking at a temperatures greater than 245 degrees F, having medicinal benefits distinct from THC. |
| Δ-9 Tetrahydrocannabivarin | Anti-inflammatory, anticonvulsant, analgesic, antioxidant, neuroprotective (Parkinson's disease model), improves insulin sensitivity, and glucose tolerance. |
| Δ-8 Tetrahydrocannabinol | Less psychotropic than THC, stimulates appetite. |
| Δ-8 Terachydrolcannabinolic Acid | Not well studied. |
| Tetrahydrocannabivarin (THCV) | Euphoriant, analgesic. |
| Cannabinol (CBC) | Sedative, antibiotic, anticonvulsant, anti-inflammatory. |
| Cannabidiol (CBD) | Antianxiety, anticonvulsant, antipsychotic, antispasmodic, may be useful in the treatment of Parkinson's, Huntingdon's and Alzheimer's diseases, multiple sclerosis and addiction, and has demonstrated efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA). |
| Cannbidiolic Acid (CBDA) | Antibiotic. |
| Cannabichromene (CBC) | Antibiotic, antifungal, anti-inflammatory, analgesic, antidepressant, and anandamide reuptake inhibitor. |
| Cannabigerol (CBG) | Antibiotic, antifungal, GABA uptake inhibitor, antidepressant, analgesic, and anti-inflammatory. |
| Cannabigerolic Acid (CBGA) | Antibiotic. |
| Cannabidivarin(CBDV) | Anticonvulsant. |
| Cannabinol (CBN) | Possible degradation product of THC or CBD, CBN is a sedative, useful activity against MRSA and reduces scaling in psoriasis. |

| Synthetic Cannabinoids | |
|---|---|
| Sativex (Nabixomols) | Combination of natural THC and CBD extracts in a mouth spray, relieves spasticity of multiple sclerosis, approved in the U.K. |
| Marinol, Dronabinol | Synthetic THC used for nausea and vomiting in cancer patients, stimulates appetite and eases neuropathic pain. |
| Nabilone, Cesamet | Synthetic THC used for nausea and vomiting in cancer patients. |
| Dexanabinol | Synthetic nonpsychotropic that blocks NMDA receptors and COX2-mediated cytokines and is neuroprotective (TBI). |
| CT-3 (Ajulemic Acid) | Synthetic, more potent analogue of THC used for neuropathic pain and spasticity. |
| Cannabinor (formerly PRS-211, 375) | Synthetic CB2 agonist for neuropathic and chronic pain, anti-inflammatory. |
| HU 308 | Synthetic that binds CB2 for hypertension and is an anti-inflammatory. |
| HU 331 | Synthetic that binds CB1, CB2 and has non-CB receptor-mediated effects for treatment of weight and appetite loss, analgesia, neurodegenerative disease, and inflammation. |
| Rimonabant/Acomplia | Synthetic that blocks endocannabinoid activity in the brain and suppresses appetite. |
| Taranabant/MK-0364 | Blocks CB1, suppresses appetite. |

through various cell-signaling pathways, triggering apoptosis, inducing differentiation, and inhibiting angiogenesis and tumor cell invasion.

*Nausea and Vomiting*

Synthetic cannabinoids are approved for the use of vomiting and nausea in which conventional antiemetics have not been effective. In a review of 1,366 patients, cannabinoids were found to be more effective than the conventional antiemetics prochlorperazine (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45232&version=Patient&language=English*,) metoclopramide (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45225&version=Patient&language=English*), chlorpromazine, thiethylperazine (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=467870&version=Patient&language=English*), haloperidol (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=476306&version=Patient&language=English*), domperidone, and alizapride. However, cannabinoids were not more effective for those receiving very low or very high dose emetogenic (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=454776&version=Patient&language=English*) chemotherapy.

*Analgesia*

Cannabinoids are effective in the control of both acute and chronic pain by modulating nociceptive signals in the central and peripheral nervous systems. Only CB1 agonists exert analgesic (http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45590&version=Patient&language=English) activity in the CNS. Both CB1 and CB2 agonists have analgesic activity in peripheral tissue. The effects of CBD may be primarily anti-inflammatory and appear at least partially to involve a T-cell suppressive effect.

*Appetite*

Of particular interest to nutritionists is the effect of cannabis on appetite. Cannabinoids appear to affect appetitive and consumatory behavior. The endocannabinoid system is involved in both the homoeostatic (sensing of deficient energy balance and gastrointestinal load) and hedonic (sensing of the salience and the motivational value of nutrients) aspects of food intake. Cannabinoid-induced hyperphagia has been clearly linked to CB1 receptor activation. In addition, cannabinoid effects may have some interaction with opioid and serotonergic systems. THC-induced hyperphagia, for instance, can be attenuated by the administration of naloxone. Orexigenic effects of CB1 agonists and inhibitors of degradation are exerted by CB1-mediated stimulatory and inhibitory effects on hypothalamic orexigenic and anorectic neuropeptides, respectively. Orexigenic effects are also facilitated by dopamine release and by regulating the activity of sensory and vagal fibers in brainstem-duodenum neural connections. CB1 receptors in the brain are under the control of leptin, ghrelin and glucocorticoids in the hypothalamus, under the dopamine in the limbic forebrain, and under the cholecystokinin and ghrelin in the brain stem.[24] Farrimond et al.[25] have also shown that non-Δ-9-THC cannabinoids lead to increased food intake in rats.

THC has been investigated for appetite stimulation in people with advanced cancer and HIV. In one small trial, Dronabinol administration led to improved food intake. Patients reported that food tasted better, and the proportion of calories (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44651&version=Patient&language=English*) consumed as protein (*http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46092&version=Patient&language=English*) was greater than in the placebo recipients. The results of older trials showed that cannabis led to increased food intake as snacks, particularly of fatty and sweet foods.

*Inflammatory Bowel Disease (IBD)*

THC and CBD have potentially beneficial effects at the level of the gut. Activation of CB2 receptors has significant anti-inflammatory effects, and CB1 receptors prevent overstimulation of intestinal motility. THC may help reduce intestinal permeability, and the expected antiemetic, analgesic and psychotropic effects may also benefit IBD patients.[26]

Proposed Clinical Uses for Cannabis

- Anorexia — THC
- Nausea — THC, CBD (not responsive to 5-HT3 antagonists, Dronabinol, Nabilone)
- Pain, Inflammation — CBD, THC
- Appetite Suppression — THCV, synthetic CB1 antagonists
- Epilepsy/Seizure Disorders — Primarily CBD, THCV
- Anxiolytic — CBD
- Neuroprotetction — CBD
- Antiemetic — CBD
- DM (Diabetes Mellitus) — CBD
- Inflammatory Bowel Disease — CBD, THC
- Bone Formation
- Glaucoma
- Cancer — THC, CBD
- Antimicrobial — CBD, CBG

In contrast to how we use most drugs, cannabis users take advantage of plant complexity and synergism by using the whole plant rather than single compounds (called the entourage effect). Approximately 40% of the cannabinoid content of cannabis is CBD, which binds CB2 receptors preferentially as well as 5HT1A receptors. Other terpenoids (of which there are over 200 in the plant) further modulate the effect of THC and CBD. In people, a THC:CBD ratio of 1:1 is usually suggested for both pain relief and appetite stimulation. For extreme pain, a ratio of 3:1 is preferred. Low THC strains are used most often for conditions such as post-traumatic stress disorder (PTSD) and dementia.

*Dosing*

In people, oral availability is low (6 to 20%), and absorption via inhalation is higher. Anecdotal data suggests that CBDs may be administered to dogs at dose ranges from



From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.

0.1 mg/kg/day to 10 mg/kg/day based on studies in multiple species.

Dr. Dawn Boothe, director of the Clinical Pharmacology Laboratory at Auburn University, is currently (January 2016) recruiting dogs being administered cannabis for determination of blood cannabinoid levels.

*Regulatory Status*

In the U.S., marijuana was banned in 1937, and the federal law was reversed in California in 1996. Cultivation of even hemp in the U.S. was illegal until the Farm Bill of 2014 was passed. Although cultivation of marijuana is legal in some states, federal regulatory status of the plant is quite different. In some U.S. states, the cultivation of hemp is illegal but cultivation of marijuana is not, and likewise in other states, medicinal use of marijuana is legal and cultivation and transport over state lines is not. The following websites detail the regulatory status of marijuana state by state:

NORML: *norml.org/states*

PRO-CON: *medicalmarijuana.procon.org/view.resource.php?resourceID=000881*

GOVERNING: *www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html*

Cannabis is a DEA Schedule I drug (no medicinal use with high abuse potential), along with heroin, LSD and Ecstasy. On the other hand, Marinol (a synthetic THC) is a Schedule III drug. Nonetheless, 23 states and the District of Columbia have legalized cannabis for limited medicinal uses for humans. Colorado and Washington state have additionally legalized recreational cannabis for people over the age of 21. Although pet owners are allowed to administer cannabis to their animals, veterinarians in all states are prohibited from prescribing it. There is federal legislation pending in Congress to reschedule cannabis.

CBD is available legally if it is obtained from industrial hemp plants rather than medical marijuana. Examples of legal CBD products include HempRx from Rx Vitamins, Treatables, Canna Companion and Canna-Pet. Dosing has not been established and likely depends on the condition being treated, individual genetic and metabolic factors, and the THC:CBD ratio being used.

Although veterinarians cannot recommend cannabis, they can assist clients in the following ways:

- Advise on toxicity, as dogs have a higher number of brain receptors for cannabinoids potentially making them more sensitive to cannabis compared to people.
- Discuss legal cannabis options in which high CBD products may be appropriate.

*Toxicity*

In people, cannabis is considered safe and has been shown to be nonaddictive. Reports are increasing in the literature of cannabis toxicity, especially in dogs. Presumably this is from deliberate or accidental ingestion due to the palatability of new edibles, but cannabis is cited as a common toxicological risk for police dogs in the line of duty.

Cannabis is absorbed rapidly after oral or inhalant administration. Although signs of toxicity may be observed within 30 to 60 minutes, onset may be as long as 12 hours after exposure. Sedation/depression, hypotension, vomiting, altered behavior, ataxia, tachycardia, bradycardia, hypersalivation, hypothermia, weakness, and seizures may be observed. THC has a long half-life due to enterohepatic circulation. Supportive treatment with benzodiazepines, phenothiazines and antiemetics may be needed. Elimination via hepatic metabolism and biliary excretion is complete in five days in dogs.

Dogs have the highest concentrations of CB1 receptors in the cerebellum of all species examined to date. This research was performed in the 1970s by the Department of Defense, seeking the possibility of weaponizing cannabis.

Regarding toxicity, the LD50 is high at 3 g/kg. The minimum dose to create static ataxia in the dog is 0.5 mg/kg of THC IV. Dogs develop tolerance to THC after repeated administration.

Unanswered questions include:

- Relevant drug interactions
- Quality control/purity/potency
- Species differences in metabolism
- Paradigm issues in which this is the only medicinal drug smoked
- Regulatory issues have hindered research

## Dietary Supplements: Regulation and Monitoring

*The Human Supplement Industry*

Since the establishment of the Dietary Supplement Health and Education Act (DSHEA) in 1994, the dietary supplement industry has grown from around $6 billion in annual sales to more than $35 billion in sales in 2014, according to estimates from the *Nutrition Business Journal*.

The Council for Responsible Nutrition recently announced an initiative to develop a voluntary dietary supplement registry that will help regulators gain more visibility to products. Trade associations representing the dietary supplement industry wrote a letter expressing collective support for the elevation of the Division of Dietary Supplement Programs (DDSP) to an "office" status within the Food and Drug Administration's (FDA) Center for Food Safety and Applied Nutrition (CFSAN).

The groups submitting the request include the American Herbal Products Association (AHPA), Consumer Healthcare Products Association (CHPA), Council for Responsible Nutrition (CRN), Natural Products Association (NPA), and United Natural Products Alliance (UNPA). These groups reported, "The Secretary of Health & Human Services has recently notified Congress of its desire to implement this

reorganization within FDA, and we endorse this change on behalf of our members as well."

It was a tough year for the industry in 2015.[27] The New York attorney general's office conducted an investigation of dietary supplements obtained from various large outlets. The supplements were analyzed using DNA barcoding technology.

The report concluded: Using DNA barcoding technology to examine the contents of herbal supplements, the attorney general's investigation is focused on what appears to be the practice of substituting contaminants and fillers in the place of authentic product. The investigation looked at six herbal supplements sold at the four major retail companies across the state.

While overall 21% of the product tests confirmed DNA barcodes from the plant species listed on the labels, 35% of the product tests identified DNA barcodes from plant species not listed on the labels, representing contaminants and fillers, and 79% were negative for DNA related to the labeled content or verifying contamination with other plant material. A large number of the tests did not reveal any DNA from a botanical substance of any kind. Some of the contaminants identified include rice, beans, pine, citrus, asparagus, primrose, wheat, houseplant, wild carrot, and others. In many cases, unlisted contaminants were the only plant material found in the product samples.

New York Attorney General Eric Schneiderman sent cease and desist letters letters to the following manufacturers: Nutraceutical International Corp. (Solaray); Alternative Remedies Health & Herbs; The Kroger Co. (parent of Vitacost.com); FoodScience Corp. (Food Science of Vermont & DaVinci Labs); Biopower Nutrition; Thorne Research Inc.; NBTY Inc. (Puritan's Pride); Olympian Labs Inc. (Prescribed Choice); Now Foods; Nature's Sunshine Products Inc.; RHG & Co. Inc. (Vital Nutrients); The Natural Healing Room & End Time Essentials; and Shine Supplements.

*Industry Response*

A response to the New York attorney general's report was commissioned by four trade associations representing the dietary supplement industry[28]: AHPA, CHPA, CRN, and UNPA. The report illustrates the following flaws in the New York attorney general's report:

1. Most, if not all, of the material containing cells (with the DNA) is typically removed during extraction (or at the very least, damaged), leaving the phytochemicals but not the DNA in the finished product.
2. Specialized training and extensive experience in the field of plant-species identification on top of a solid understanding of the various processing and extraction techniques used by each manufacturer are necessary to obtain reliable results from testing botanical dietary supplements.

*Industry Future*

Trends

- New delivery forms to mask bitter tastes, deliver time-release substances or enhance bioavailability.
- Renewed attention to adulterated products and self-policing. Appropriate testing at all stages in manufacturing and the transparency of label information. Quality, safety, efficacy, sustainability, and transparency will become more than just buzzwords.
- China passed a new Food Safety Law that provides a framework for new dietary supplement policy. These new supplement regulations aim to streamline the system and make bringing products to market more transparent. There will be a recording system for nutritional supplements such as vitamins, minerals and other yet-to-be-determined nutrients. China's Food and Drug Administration (CFDA) and National Health and Family Planning Commission are currently creating a list of ingredients that will be allowed in supplements.
- Some large retailers are raising liability insurance requirements for their supplement suppliers. For example, KeHe Distributors recently required a minimum of $5 million coverage from its suppliers.

**NASC**

The National Animal Supplement Council (NASC) is a trade organization formed to "self-police" the animal supplement industry. It states, "NASC's overriding goal is to promote the health and well-being of nonhuman food-chain animals that are given animal health supplements by their owners, and to protect and enhance the integrity of the animal health product industry."

Members of the NASC undergo an audit before they are given full membership and allowed to display the NASC seal. The NASC enforces Good Manufacturing Practice Quality Standards in manufacturing, labeling and marketing animal health supplements and has established an adverse event monitoring system to which members are required to adhere.

NASC represents a more stringent quality control and adverse event reporting system than is available for even the human supplement industry. Consumers desiring more reliable products should consider purchasing only products with the NASC label.

## References

1. Aggarwal BB, Yuan W, Li S, et al. Curcumin-Free Turmeric Exhibits Anti-Inflammatory and Anticancer Activities: Identification of Novel Components of Turmeric. *Mol Nutr Food Res*. 2013;57(9):1529-1542.



From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.

2. Peddada KV, Peddada KV, Shukla SK, et al. Role of Curcumin in Common Musculoskeletal Disorders: A Review of Current Laboratory, Translational, and Clinical Data. *Orthop Surg*. 2015;7(3):222-231.

3. Panahi Y, Saadat A, Beiraghdar F, et al. Adjuvant Therapy with Bioavailability-Boosted Curcuminoids Suppresses Systemic Inflammation and Improves Quality of Life in Patients with Solid Tumors: A Randomized Double-Blind Placebo-Controlled Trial. *Phytother Res*. 2014;28(10):1461-1467.

4. Khajehdehi P, Zanjaninejad B, Aflaki E, et al. Oral Supplementation of Turmeric Decreases Proteinuria, Hematuria, and Systolic Blood Pressure in Patients Suffering from Relapsing or Refractory Lupus Nephritis: A Randomized and Placebo-Controlled Study. *J Renal Nutr*. 2012;22(1):50-57.

5. Khajehdehi P, Pakfetrat M, Javidnia K, et al. Oral Supplementation of Turmeric Attenuates Proteinuria, Transforming Growth Factor-β and Interleukin-8 Levels in Patients with Overt Type 2 Diabetic Nephropathy: A Randomized, Double-Blind and Placebo-Controlled Study. *Scand J Urol Nephrol*. 2011;45(5):365-370.

6. Prasad S, Tyagi AK, Aggarwal BB. Recent Developments in Delivery, Bioavailability, Absorption and Metabolism of Curcumin: The Golden Pigment From Golden Spice. *Cancer Res Treat*. 2014;46(1):2-18.

7. Campbell-Mcbride N. Gut and Psychology Syndrome: Natural Treatment for Autism, ADD/ADHD, Dyslexia, Dyspraxia, Depression. *Schizophrenia*. Cambridge, MA: Medinform Publishing. 2010.

8. McCance RA, Sheldon W, Widdowson EM. Bone and Vegetable Broth. *Arch Dis Child*. 1934;9(52):251-258.

9. Monro JA, Leona R, Purib BK. The Risk of Lead Contamination in Bone Broth Diets. *Med Hypotheses*. 2013;80(4):389-390.

10. Pandita KK, Pandita S, Hassan T. "Toxic" Beef Bone Soup. *Clin Cases Miner Bone Metab*. 2011;8(2):43-44.

11. Hesslink R, Armstrong D, Nagendran MV, et al. Cetylated Fatty Acids Improve Knee Function in Patients with Osteoarthritis. *J Rheumatol*. 2002;29(8):1708-1712.

12. Kraemer WJ, Ratamess NA, Maresh CM, et al. Effects of Treatment with a Cetylated Fatty Acid Topical Cream on Static Postural Stability and Plantar Pressure Distribution in Patients with Knee Osteoarthritis. *J Strength Cond Res*. 2005;19(1):115-121.

13. Kraemer WJ, Ratamess NA, Maresh CM, et al. A Cetylated Fatty Acid Topical Cream with Menthol Reduces Pain and Improves Functional Performance in Individuals with Arthritis. *J Strength Cond Res*. 2005;19(2):475-480.

14. Kraemer WJ, Ratamess NA, Anderson JM, et al. Effect of a Cetylated Fatty Acid Topical Cream on Functional Mobility and Quality of Life of Patients with Osteoarthritis. *J Rheumatol*. 2004;31(4):767-774.

15. Singh SS, Wang H, Chan YS, et al. Lectins from Edible Mushrooms. *Molecules*. 2015(20):446-469.

16. Lindequist U. The Merit of Medicinal Mushrooms from a Pharmaceutical Point of View. *Int J Med Mushrooms*. 2013;15(6):517-523.

17. Jin X, Ruiz Beguerie J, Sze DM, et al. *Ganoderma lucidum* (Reishi Mushroom) for Cancer Treatment. *Cochrane Db Syst Rev*. 2012;13;6.

18. Elsayed EA, Enshasy HE, Wadaan MA, et al. Mushrooms: A Potential Natural Source of Anti-Inflammatory Compounds for Medical Applications. *Mediat Inflamm*. 2014. http://dx.doi.org/10.1155/2014/805841

19. Paterson RR, Lima N. Biomedical Effects of Mushrooms with Emphasis on Pure Compounds. *Biomed J*. 2014;37(6):357-368.

20. Brown DC, Reetz J. Single Agent Polysaccharopeptide Delays Metastases and Improves Survival in Naturally Occurring Hemangiosarcoma. *Evid-Based Compl Alt*. Epub: Sept. 5, 2012. doi: 10.1155/2012/384301.

21. Silver R. Medical Marijuana Update: New Research, Changes in Regulatory Environment and Options for Vets in Practice. *Annual Conference of the American Holistic Veterinary Medical Association*. Augusta, GA. 2015.

22. Boothe D. The High Points of Medical Marijuana. Atlantic Coast Veterinary Conference. 2014.

23. Cannabis and Cannabinoids — For Health Professionals (PDQ®). National Cancer Institute at the National Institutes of Health. *http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq*

24. Di Marzo V. The Endocannabinoid System: Its General Strategy of Action, Tools for Its Pharmacological Manipulation and Potential Therapeutic Exploitation. *Pharmacol Res*. 2009(Aug);60(2):77-84.

25. Farrimond JA, Whalley BJ, Williams CM. Non-Δ⁹Tetrahydrocannabinol Phytocannabinoids Stimulate Feeding in Rats. *Behav Pharmacol*. 2012;23(1):113-117.

26. Naftali T, Mechulam R, Lev LB, et al. Cannabis for Inflammatory Bowel Disease. *Digest Dis*. 2014;32(4):468-474.

27. A.G. Schneiderman Asks Major Retailers to Halt Sales of Certain Herbal Supplements as DNA Tests Fail to Detect Plant Materials Listed on Majority of Products Tested. New York Attorney General's Office. 2015. *http://www.ag.ny.gov/press-release/ag-schneiderman-asks-major-retailers-halt-sales-certain- herbal-supplements-dna-tests*. (Accessed Dec. 13, 2015)

28. Reynaud DTH. The Capabilities and Limitations of DNA Barcoding of Botanical Dietary Supplements. 2015. *http://www.crnusa.org/NYAG/The-Capabilities-and-Limitations-of-DNA-Testing-FINAL-3-10-2015.pdf* (Accessed Dec. 13, 2015)



From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.