



**Natural • Organic • Holistic**

**TECHNICAL DATA  
AND  
RESEARCH MATERIAL**

Volume II

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# **Natural Pain Relief , Fever Relief and Anti-Inflammatory,** For Dogs

## **White Willow Bark** All Natural Pain Relief

### **White Willow Bark**

Other Names: Salix alba, white willow, willow bark

Salicin, the major salicylate compound in willow bark, effectively delivers salicylic acid into the bloodstream, but it does this in a unique way. Salicin is carried unchanged (and hence is stomach friendly) to the distal ileum or colon where gut flora remove the sugar and convert it into salicyl alcohol. The salicyl alcohol is absorbed and oxidized in the blood, tissue and liver to give salicylic acid. Salicin provides a more sustained release of salicylate than sodium salicylate itself. (9)

White willow bark is an all natural source that reduces pain, fevers, and inflammation. The medicinal use of willow bark dates back to the Greek physician Hippocrates (400 B.C.), who advised his patients to chew on willow bark to reduce pain, fever and inflammation. William Wallace of famed “Brave Heart” was offered white willow prior to his tortures execution.

Natural White Willow Bark is a canine safe ingredient from a tree native to Europe and Asia. The name "white willow" comes from the color of the leaves, which are covered with fine white hairs.

In 1829, scientists in Europe identified what was believed to be the active ingredient in white willow bark—a compound called salicin. Public demand grew rapidly. The German company Bayer eventually created a synthetic derivative of salicylic acid, called acetylsalicylic acid (ASA), and mass-produced it under the name aspirin.

Aspirin should not be given to a canine in any shape or form buffered or otherwise . Studies have proven Aspirin thins the dogs blood which can be life threatening if the dog receives a cut or has internal bleeding and can also cause severe liver damage. Aspirin is still known for irritating the stomach lining.

### **Salicin versus Synthetic Aspirin**

The Differing Pharmacologies of the Salicylate Derivatives Many articles seem to regard willow bark as a kind of herbal aspirin. But there are important differences between the salicylate compounds in willow bark and aspirin, as can be seen from the chemical diagrams below.

In terms of pharmacology, aspirin is a potent inhibitor of COX-1 and COX-2 because it causes irreversible acetylation of COX, which completely inactivates this enzyme system. Aspirin therefore has potent analgesic and anti-inflammatory activities (COX-2) but also can cause gastric damage and inhibit platelet function (COX-1).

Platelet function is affected by the inhibition of production of thromboxane A2 (a prostaglandin) by COX-1. Because aspirin irreversibly inactivates COX by acetylation and because platelets cannot make new

### **Salicin versus Synthetic Aspirin cont.**

proteins such as COX (no nucleus), the effect of aspirin persists for the life of the platelet (7 to 10 days). Even low doses of aspirin can therefore have profound blood-thinning effects.

Unlike aspirin, salicylic acid has virtually no inhibitory effect on isolated COX-1 or COX-2. However it can inhibit PG synthesis in intact cells. This means that salicylic acid or sodium salicylate will have little antiplatelet (blood thinning) effects -- they lack the acetyl group. However a high dose of salicylic acid will still irritate the stomach, but this is because it is a phenol, not because of any effects on COX.

Although it has little direct effect on COX-2 once it is formed, salicylic acid could exert anti-inflammatory and analgesic activity by inhibiting COX-2 induction. Recently, it has been reported that aspirin and sodium salicylate equipotently suppress COX-2 induction at therapeutic concentrations. Also salicylates appear to have direct analgesic effects in the CNS by unknown mechanisms. (1)

### **Pharmacokinetics**

Salicin derivatives (e.g. salicortin, tremulacin) are first converted into salicin in the dog's stomach or small intestine. Salicin is then mainly carried to the distal ileum or colon where gut flora convert it into its aglycone (salicyl alcohol). Salicyl alcohol is absorbed and oxidized in blood, tissue and liver to form salicylic acid. Salicylic acid is then converted to salicylic acid conjugates or to gentisic acid by hepatic transformation for excretion via the urine. From the excretion data it was concluded that 86% of an administered dose of salicin was absorbed. (24,25) A 4-gram oral dose of salicin was rapidly metabolized, reaching a peak plasma level of salicylate in just under 2 hours. This peak plasma level was maintained for several hours. Comparison of the salicylate plasma levels obtained from both sodium salicylate and salicin demonstrated that the curve for salicin is slightly lower and flatter, indicating a greater half-life for salicin. The maximum plasma concentration of free salicylate from 4 g of salicin was 100 [micro]g/mL, whereas 2 g of sodium salicylate yielded 150 [micro]g/mL. (24)

### **Toxicology**

There is no information available on the toxicology of White Willow Bark. The toxicity of salicylates is well documented. An overdose resulting from acute ingestion of 6.5-9.8 g of aspirin usually produces a serum salicylate level of 300 (micro)g/mL or greater. From the pharmacokinetic study given previously, more than 50 g/ day of salicin would need to be ingested in order to achieve this blood level of salicylate. White Willow Bark proves to be a vastly safer pharmacokinetic.

## **Yucca Schidigera**

Yucca's greatest nutritive and healing powers are chiefly attributable to its impressive content of saponin compounds. Herbalists and mainstream medical researchers recognize saponins for their anti-inflammatory, antifungal and stimulatory functions in the body. Saponins, precursors of cortisone, prevent the release of toxins from the intestines that restrict normal cartilage formation. Saponins are produced naturally in the body by the adrenal glands. It is believed yucca works best for arthritis when taken over an extended time. It is reported to speed up bowel elimination, reduce fecal and urine odor, and improve digestion in dogs and cats.

In a study conducted at the beginning of the twentieth century, the "saponin extract" from the "desert yucca plant" was found to bring safe and effective relief (from pain and inflammation) to human arthritis patients when taken four times daily over a period of time.

## **Boswellia and Yucca as Alternatives to Phenylbutazone**

Karen Briggs reports: “Alicia Bertone, DVM, Ph.D., and her team at Ohio State University has given us another reason to be cautious about the long-term use of bute (phenylbutazone). In the study by OSU’s Orthopedic Research laboratory, 11 sound 18-30 month- old horses were given oral doses of phenylbutazone (at a rate of 4.4

mg per kilogram of body weight) over a 14- day period. Joint cartilage specimens were harvested from each animal at the start of the study, after 14 days of treatment, and two weeks after drug administration ceased, and examined each time for indicators of proteoglycan synthesis. Proteoglycan synthesis was found to be significantly reduced in the cartilage specimens, as compared to cartilage taken from a control group who received no bute. OSU researchers concluded that long-term administration of bute can interfere with equine joint cartilage regeneration.

In a previous paper published in the May, 2000 issue of the *American Horse Journal of Veterinary Research*, Bertone and her team also outlined the detrimental effects of bute on bone formation and activity in healthy yearlings and two-year-olds. In all six of the study horses who received bute for two weeks, there was a marked decrease in bone mineralization and a decreased healing rate when bone biopsies were performed on the tibia.

## **Connective Tissue**

Flexible tissues like connective tissue and cartilage contain proteins with flexible sulfur bonds. Collagen is the most abundant protein in the body, and a major component of all connective tissue. In skin, collagen works with fibers of another protein called elastin, to give skin its elasticity. In cartilage, the sulfur containing proteoglycans glucosamine and chondroitin form with collagen, a fibrous protein substance that gives cartilage its structure and flexibility. Researchers at Oregon Health Sciences University studied a strain of mice that were prone to the spontaneous development of joint lesions similar to those in rheumatoid arthritis. They found that animals that were fed a diet that included a 3% solution of MSM as drinking water from the age of two months until the age of five months suffered no degeneration of articular cartilage. In a control group of mice receiving only tap water, 50% of the animals were found to have focal degeneration of articular cartilage. Especially in combination with vitamin C, MSM has demonstrated remarkable ability to reduce or eliminate the incidence of muscle soreness.

## **Metabolism**

Sulfur bridges are responsible for the spatial structure of enzymes. Without sulfur bridges, enzymes would lack biological activity due to deviations in their spatial structure. Shortages in sulfur cause reduced production of biologically active enzymes, which result in a reduction of many metabolic processes. Sulfur is important for the cellular energy production in which glucose is metabolized under the release of energy.

Most important, sulfur plays a role in the electron transport system, as part of iron/sulfur proteins in mitochondria, the energy factories of the cell. Furthermore, sulfur participates in the vitamin B Thiamine (B1) en Biotin. These vitamins are essential for converting carbohydrates into energy, by burning glucose. Insulin is a hormone excreted by the pancreas which mainly functions to regulate the blood sugar level. Insulin therefore plays an important role in the carbohydrate metabolism. Each insulin molecule consists of two amino acid chains, connected to one another by sulfur bridges. These sulfur bridges are very important for the proper functioning of insulin. Without these bridges, the hormone loses its biological activity.

MSM allows the body to more effectively take up oxygen. In the first place, it improves the elasticity of the lung cells and the permeability of long cell membranes, allowing more air to be breathed and oxygen to pass through the membranes into the blood stream. Secondly, MSM prevents and corrects the clotting of red blood cells, allowing the blood to absorb more oxygen. Moreover, by improving the cell membrane permeability, cells throughout the body can take up more oxygen from the blood, and hence produce more energy.

MSM is considered a potentiator of most vitamins and other nutrients, such as vitamin C, Coenzyme Q10, all B-vitamins, vitamin A, D and E, amino acids, selenium, calcium, magnesium and many others. MSM improves the cellular uptake of these nutrients, and prolongs their lives. The body can better utilize the nutrients, so taking dietary supplements is more efficient.

## **Parasites**

MSM has an anti-parasitic action against *Giardia*, *trichomonas*, roundworms, nematodes, *Enterobius* and other intestinal worms. Animal studies include laboratory mice, determined to have pin worms (*Enterobius*) by fecal cast examination. They were given commercial food and drinking water, both containing 2% MSM by weight. After 17 days, fecal examination indicated the feces were free of worms and eggs. The blood level of MSM in one animal examined exceeded 30 ppm or mg/kg. The major antiparasitic property of MSM is probably caused by its ability to bind to the mucosa and present a natural blocking interface between hosts and parasites. It's as though MSM puts down a coating on the mucosa, which parasites find impenetrable and can't cling to. Unable to stick, the parasites are simply flushed out of the body. In vitro research has shown the antiparasitic, antifungal and antibacterial action of MSM concentrations. MSM concentrations of 1 mg/mL and less demonstrated no significant inhibition of *Giardia lamblia*. However, at 20 mg/mL concentrations it was strongly inhibitory, and concentrations above 40 mg/mL promptly killed the organism. According to Dr. Herschler, one can safely administer up to 1-2 gram MSM per kg body weight on a daily basis. One therefore builds a safely tolerated blood level up to 4000 ppm (mg/kg), which level is highly toxic to many infective organisms yet is harmless to the host.

## **Autoimmune Diseases**

MSM very effectively fights inflammations resulting from autoimmune reactions. In an experiment, a special strain of mice was studied that is prone to the spontaneous development of rheumatoid arthritis-like joint lesions. Mice prone to the development of Autoimmune Lymphoproliferative Disease (ALD) were fed a diet that included a 3% solution of MSM as drinking water from the age of one month. The mean life span of the control group was 5.5 months, whereas the mean life span of the MSM group was extended to more than 10 months of age. The MSM group showed decreased anti-nuclear antibody responses and significant diminution of lymphadenopathy, splenomegaly and anemia development, thus suggesting that MSM provided significant protection against the development of the autoimmune disease ALD. Other experiments were conducted on mice bred for their propensity to acquire the autoimmune disease Systemic Lupus Erythematosus (SLE).

These experiments showed MSM to have a protective effect both before and after the onset of the disease. Mice which are maintained on a diet including 3% MSM in their drinking water from age one month, suffered lower death rates and liver damage than control groups drinking only tap water. After seven months 30% of the control group had died, while all the MSM mice were still alive. Also, when mice seven months old and already showing signs of advanced lupus were fed the MSM diet, 62% of the animals were still alive after nine months compared to 14% for the control group that received only tap water.

## **Diabetes**

The sulfur-containing B vitamin biotin is a critical part of glucokinase, the enzyme involved in the utilization of the sugar glucose. Sulfur is also a component of insulin, the protein hormone secreted by the pancreas that is essential to carbohydrate metabolism. Lack of nutritional sulfur in the diet can result in low production of biological active insulin. Studies indicate that MSM improves cellular glucose uptake by improving cell permeability, thus balancing blood sugar levels and returning the pancreas to normal functioning.

## **Toxicology**

MSM is considered to be one of the least toxic substances in biology, similar in toxicity to water. When MSM was administered to human volunteers, no toxic effects were observed at intake levels of 1 gram per kg of body weight per day for 30 days. Intravenous injections of 0.5 grams per kg body weight daily for five days a week produced no measurable toxicity in human subjects. The lethal dose (LD50) of MSM for mice is more than 20 g/kg body weight.

MSM has been widely tested as a food ingredient without any reports of allergic reactions. An unpublished Oregon Health Sciences University study of the long-term toxicity of MSM over a period of six months, showed no toxic effects. More than 12,000 patients were treated with MSM at levels above two grams daily, without toxicity.

## **Natural Joint Supplements** **For dogs**

Common joint problems occur as a result of damage done to cartilage and synovial fluid. To effectively address these joint problems, there are three elements necessary to repair cartilage and synovial fluid:

- 1.) Collagen
- 2.) Proteoglycans
- 3.) GAGs (Glycosaminoglycans)

In order to accomplish this with nutrients, removal of the damaging free radicals and inflammation that inhibit the regeneration process must also be addressed. These tasks can be accomplished with the following ingredients:

- 1.) **Chondroitin Sulfate** - Contains 90% GAGS and is 95% pure. GAGS are the necessary glycosaminoglycans. **Chondroitin sulfate** is a sulfated [glycosaminoglycan](#) (GAG) composed of a chain of alternating sugars ([N-acetylgalactosamine](#) and [glucuronic acid](#)). It is usually found attached to proteins as part of a [proteoglycan](#). Chondroitin sulfate is an important structural component of [cartilage](#) and provides much of its resistance to [compression](#) <sup>[1]</sup>. Along with [glucosamine](#), chondroitin sulfate has become a widely used [dietary supplement](#) for treatment of [osteoarthritis](#).
- 2.) **Glucosamine HCL** - Builds GAGs, collagen, and proteoglycans. **Glucosamine HCL** is an [amino sugar](#) and a prominent precursor in the [biochemical](#) synthesis of [glycosylated](#) proteins and lipids. A type of glucosamine forms [chitosan](#) and [chitin](#), which composes the exoskeletons of [crustaceans](#) and other [arthropods](#), cell walls in [fungi](#) and many higher organisms. Glucosamine is one of the most abundant [monosaccharides](#). Glucosamine is commonly used as a treatment for [osteoarthritis](#).
- 3.) **Yucca** - Remove inflammation and the pain caused by inflammation. Boswellia has been shown in studies to remove inflammation more effectively than phenylbutazone. **Yucca contains natural** steroidal-like saponins that are effective

anti-inflammatory and anti-spasmodic which are known to reduce pain associated with arthritis.

- 4.) **Ester-C® Calcium Ascorbate** (*Source of Vitamin C*)  
Water-soluble antioxidant that removes damaging free radicals.
- 5.) **Vitamin E** - Fat soluble antioxidant that removes damaging free radicals.

**Digestive enzymes and probiotics have been added, in a proportionate amount, to aid in the utilization of the above ingredients. Additional digestive enzymes may be given during meal feedings.**

## **Joint Support Ingredients** **Glucosamine HCL**

Glucosamine provides joints with the building blocks needed to repair damage caused by osteoarthritis or injuries. Specifically, the Glucosamine provides the raw material needed by the body to manufacture a mucopolysaccharide (glycosaminoglycan) found in cartilage, collagen and proteoglycans. Glucosamine may also play a role in wound healing.

### **Glucosamine is Valuable**

Chondrocytes either obtain Glucosamine preformed from the circulation, or synthesize it from glucose and amino acids. Regardless of the source, Glucosamine levels are critical to subsequent macromolecular synthesis. Once Glucosamine is formed, it is used for GAG synthesis. Glucosamine is then used directly for synthesis of hyaluronan, and also for all other GAGs after conversion to other amino sugars by epimerizes. Thus, Glucosamine is more than the major building block of GAGs, it is a key up-regulator of GAG synthesis and thus cartilage matrix synthesis. **Glucosamine has been shown to stimulate GAG, and collagen synthesis in chondrocytes and fibroblasts.** Glucosamine is also the preferential substrate and a stimulant of proteoglycans biosynthesis. Furthermore, Glucosamine inhibits the degradation of proteoglycans and rebuilds the damaged cartilage.

Directly or indirectly, Glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, nails, heart valves, blood vessels, and mucous secretions of the digestive, respiratory, and urinary tracts.

Results of a clinical trial on the effects of Glucosamine were presented in November, 2000 at the 64<sup>th</sup> American College of Rheumatology meeting in Philadelphia. In a three year, randomized placebo-controlled trial recently completed at the Prague Institute of Rheumatology, Glucosamine decreased the progression of knee osteoarthritis. Results showed patients had less knee pain or stiffness, and less difficulty in performing daily activities. Their maximum walking capacity improved and the x-rays showed less narrowing of joint space.

## **Glucosamine HCL vs Glucosamine Sulfate**

On a pound per pound basis, Glucosamine HCL is more potent than Glucosamine Sulfate. The active part of both is Glucosamine. The HCL and sulfate parts are inactive. They are only present to make sure the Glucosamine will

dissolve in water. However, the sulfate part has a higher molecular weight than the HCL part. If you would add 1 gram of Glucosamine HCL to one tablet, and 1 gram of Glucosamine Sulfate to another tablet, you get more Glucosamine in the Glucosamine HCL tablet. Glucosamine HCL is 83% Glucosamine while Glucosamine Sulfate is 62.4% Glucosamine. In addition it is believed by scientists that the HCL of nutrients is more utilizable than the sulfate form. One reason is the stomachs of mammals contain HCL (Hydrochloric Acid) to help digest food. The HCL part of the Glucosamine HCL would therefore help in food digestion. The sulfate part of Glucosamine Sulfate has no digestive function.

Glucosamine Sulfate or Hydrochloride is efficiently absorbed from the gastrointestinal tract following oral intake. Glucosamine is a small molecule (m.w.=179) and is very soluble in water. Based on the fecal excretions of radioactively labeled molecules, gastrointestinal absorption of Glucosamine is about 78% in the dog, and over 81% in the rat. Evidence indicates absorption of Glucosamine by intestinal cells is carrier mediated resulting in the active transport of Glucosamine into the body. After oral consumption and absorption, Glucosamine concentrates in the liver, where it is incorporated into plasma proteins, utilized for specific biosynthetic processes, or degraded into smaller molecules. Although absorption is very high, a substantial quantity of the absorbed Glucosamine is probably modified or degraded to small compounds such as H<sub>2</sub>O, CO<sub>2</sub>, and urea as it make its "first pass" through the liver. In fact, articular cartilage concentrates Glucosamine to a greater extent than any other structural tissue. Elimination of Glucosamine is primarily in the urine, with a small amount of Glucosamine or its derivatives eliminated in the feces. Glucosamine is not readily available from any primary food source but is commercially prepared from chitin, found in shells of lobster, shrimp or crabs. Glucosamine for the most part come from crustacean shellfish such as crabs, crayfish, lobster and shrimp.

## **Glucosamine is an Amino Sugar**

Glucosamine is an amino sugar that is utilized by the body to support healthy joint structures. It is unlike other sugars in that it is incorporated into the structure of tissues rather than being used as an energy source. Glucosamine is important for the formation and maintenance of your dogs' nails, tendons, skin, eyes, bones, and heart valves. It also plays a role in the mucous secretion of the digestive, respiratory, and urinary tracts.

Pharmaceutical grade Glucosamine is ideal for your athletic dog or those with arthritis or joint pain and is very beneficial as both a preventative measure as well as for helping to combat existing problems. Glucosamine absorbs and releases water with each step and thereby acts as a shock absorber for the joints offering long-term protection for young and old dogs..

Glucosamine stimulates the formation and repair of articular cartilage. Glucosamine forms the building blocks of vital compounds called mucopolysaccharides, which are necessary for the construction and maintenance of virtually all connective tissue and lubricating fluid in the body, including tendons, ligaments, cartilage and synovial (joint) fluid.

**Method 1)** The vast majority of the Glucosamine supplied for animals are processed through poorly effective methods of crushing and cutting. Crushing employs hammer-like tools to break the solid into smaller particles by means of impact. Cutting uses sharp blades to cut the rough solid pieces into smaller ones. These inexpensive processes leave the particles in such large pieces that the ability for an animal to break them down to a usable amino sugar is extremely difficult.

It allows some manufacturers to place "Contains Glucosamine" on their packaging but the utilization is dismal at best.

**Method 2)** Traditional micronization techniques are based on friction to reduce particle size. This method includes milling and grinding using cylindrical metallic drums that usually contain steel spheres. As the drum rotates the spheres inside collide with the particles of the solid, thus crushing them into smaller diameters. In the case of grinding, the solid particles are formed when the grinding units of the device rub against each other while particles of the solid are trapped in between.

**Method 3)** Modern pharmaceutical methods use supercritical fluids in the micronization process. In this method supercritical fluid is used to dissolve the solid material under high pressure and temperature, forming a supercritical gas phase. The particles formed this way have a diameter of a few hundred nanometers. Studies show absorption rate of these particles are thousands of times better than those of crushing and hundreds of times better than grinding.

The same process is true for any of you dog owners who are personally taking Glucosamine. Make sure you too are taking only the best.

## **Collagen Type II**

HA is highly abundant in Collagen Type II, derived from 100% pure sternum cartilage of chickens. It is specially processed through a patented process to contain high concentrations of hydrolyzed collagen type II protein and low molecular weight GAG's (Glycosaminoglycans) such as Chondroitin Sulfate, Hyaluronic Acid, Glucosamine Sulfate, and other proteoglycans that readily absorb through the GI tract to allow superior bioavailability. There it can increase serum levels of amino acids specific to Collagen Type II, providing nourishment directly to the joints, thereby promoting healthy joint structure and function.

Being derived exclusively from chicken sternum cartilage, it is naturally rich in GAG's, Chondroitin Sulfate, a powerful anti-inflammatory agent and cartilage destructing enzyme inhibitor. An impressive pain reliever and an integral constituent of synovial fluid, it helps to lubricate the joints. Glucosamine, and Cartilage Matrix Glycoprotein (CMGP) also work to reduce the oxidative damage to the joints. Collagen is also an important component of bone structure. Please note that native (undenatured / not hydrolyzed) collagen type II molecule is too large to be readily absorbed into the blood stream. Only hydrolyzed Collagen Type II is capable of being readily absorbed, which ultimately leads to higher blood concentrations of GAG rich Chicken Collagen Type II in order to increase tissue concentrations to healthy levels, including joint and skin tissue to maintain a better quality of life.

## **Chondroitin Sulfate**

### **Quality of Chondroitin Sulfate**

Chondroitin Sulfate is probably the most important component of any joint formula. Research has shown that it is readily absorbed by the body. Also remember that not all chondroitin sulfates are created equally. The chondroitin sulfate used in our products is derived from beef trachea, sourced from B.S.E. FREE countries, and has a 90% GAG (glycosaminoglycan) content. Some manufacturers use chondroitin sulfate that is derived from beef cartilage or shark cartilage possessing a GAG content of between 16-22%, which is a large big difference in the active component. And this is only one of the reasons that our joint formulas are so successful.

### **Chondroitin Role in Osteoarthritis Reversal**

Osteoarthritis is a collection of ill-defined joint diseases with cartilage degeneration being a central feature. Usually deficient cartilage repair, joint bone remodeling, and later, synovial inflammatory processes promote extensive degeneration and erosion. There is substantial evidence that osteoarthritis can be reversible through chondroprotective nutrients that repair the cartilage by stimulating anabolic metabolism of chondrocytes and/or inhibiting catabolic processes found in osteoarthritis. The two major categories of chondroprotective nutrients are glycosaminoglycans and antioxidants (vitamin C, vitamin E, superoxide dismutase, and catalase). The University of

Prague, in Czechoslovakia conducted independent studies lasting five to ten years. Subjective evaluations by doctors and patients also showed significant benefits for GAG subjects. Thus, by both subjective and objective criteria, GAG treatments significantly prevented the inevitable progression to disability, and even slowed the physical findings of osteoarthritis. One study actually took cartilage biopsies before and after four weeks of oral GAG supplementation in a few treated subjects. Electron microscopy initially showed a picture of established osteoarthritis. However, after supplementation it showed a picture more similar to healthy cartilage. The results of this article strongly suggest that reversal of osteoarthritis was being accomplished after oral GAG supplementation.

## **Chondroitin Sulfate Properties**

Chondroitin Sulfate (CS) is a chondroprotective agent that is the most common glycosaminoglycan and major component of proteoglycans. A chondroprotective agent is any substance (nutrient, drug, or hormone) that enhances the ability of joint cells to repair themselves. Proteoglycans are a combination of protein and many long chains of modified sugars, usually containing sulfur. They are found everywhere in the body, especially in cartilage. Proteoglycans form a stiff gel to resist compression. Chondroitin-4-Sulfate, derived primarily from mammalian tissue, binds to the collagen in cartilage matrix, thereby contributing to the resiliency and water-holding properties of cartilage.

Another important role for CS is the activation of lipoprotein lipase on capillary endothelial cells, facilitating proper metabolism of blood lipids.

## **GAGS (Glycosaminoglycans) from Chondroitin**

Polysulfated glycosaminoglycan is a natural substance found in the chemical composition of mammalian cartilage and connective tissue. Collagen, proteins and the polysulfated glycosaminoglycans are also a potent proteolytic enzyme inhibitor and can reverse and reduce the effects of joint damage. This occurs by stimulating the secretion of joint fluid, increasing viscosity and reducing damaging protein levels in the joint. It also acts to repair damaged cartilage by forming a collagen matrix that can resist added stress. In practice, it is widely used in equine, canine and feline joint injuries. It is used worldwide in people and animals for therapy in degenerative joint disease and arthritic conditions.

## **GAGS (Glycosaminoglycans) from Chondroitin, cont.**

The use of extracted CS in arthritis and rheumatism has been demonstrated in numerous clinical studies. CS is found to have potent anti-inflammatory action and considerable immunoregulatory capability.

Per lameness expert M.J. Martinelli, DVM, PhD Dipl; ACVS, “GAGs can protect degenerating cartilage, promote the growth of new cartilage, and reverse the symptoms and damage of arthritis.” Corticosteroids and the newer oral products such as oral glucosamine and glycosaminoglycans may also help, per Wayne McIlwraith, BVSc, PhD., Dipl ACVS, Colorado State University Equine Center. McIlwraith cautions that the lack of data does not mean oral glucosamines don’t work. “I take oral glucosamine/glycosaminoglycans preparation myself for osteoarthritis in the hip.”

The healing of soft connective tissues is slow due to the fact they have either no blood supply (cartilage) or rather limited blood supply (tendons and ligaments), meaning a poor nutrient supply to those areas, even under the best conditions. Laboratory studies have found that purified chondroitin sulfates act as a naturally occurring stimulus for connective tissue cells to repair tissues. They act as precursors for synthesis of new connective tissues and importantly for arthritis, at very low concentrations, purified chondroitin sulfates can inhibit the degrading enzymes that destroy joints.

## **Chondroitin's role in Steroid and NSAIDs use**

During repair of injured connective tissue, Chondroitin Sulfate (CS) synthesis precedes collagen synthesis, and CS synthesis is essential for proper healing. Animals and humans treated with corticosteroids show decreased synthesis of CS and delayed healing. NSAIDs can cause stomach ulcers, liver disease, Cushing's syndrome, reduced resistance to infection and even diabetes. Many anti-inflammatory drugs actually damage joints, resulting in further degeneration, according to Dr. Russell Swift, D.V.M.

## **Chondroitin Molecules are Readily Absorbed**

Katsumi Murata, M.D., PhD., from the University of Tokyo, states acid mucopolysaccharides are secreted from the cell, which means it can also enter by the reverse of the process (pinocytosis). He and his colleagues performed absorption studies using S and C cleaved to Chondroitin-4-Sulfates. Both labeled products were found in the urine. The researchers have also determined that when chondroitin polysulfate is administered orally, the concentration of WHOLE (or intact) chondroitin polysulfate in the blood increased rapidly during the first 30 minutes in dogs and 90 minutes in rats. If these intact chondroitin polysulfates are found in the blood, it would be feasible to theorize that the circulatory system could take these "compounds" to the "areas in need" through either diffusion or pinocytosis. There is no basement membrane in the synovial membrane.

Following the administration of titrated chondroitin sulfate (CS) by oral and intramuscular route, the distribution of radioactivity was investigated in two opportunist omnivorous animals, namely the rat and dog. More than 70% of the orally administered radioactivity was absorbed. Independently of the administration route, radioactivity was mainly excreted through the urine. A tropism of the radioactivity was observed towards glycosaminoglycan-rich tissues, such as joint cartilage.

## **Synergistic Properties of Chondroitin Sulfate + Glucosamine**

Chondroitin-4-sulfate, derived primarily from mammalian tissue, binds to the collagen in cartilage matrix, thereby contributing to the resiliency and water-holding properties of cartilage. Over time, and as animals age, chondrocytes secrete less chondroitin-4-sulfate and more of the other forms of GAGs. This change in type of GAG concentration of the cartilage matrix has been implicated in the initiation and progression of degenerative disease processes. Glucosamine is a small glucose-like molecule found in the large proteoglycan molecules of articular cartilage, whereas chondroitin sulfate is much larger, consisting of a long chain of modified glucose molecules. Mechanism of action for Glucosamine includes increasing collagen and proteoglycan production of chondrocytes, stimulating hyaluronan production by synoviocytes, as well as possessing anti-inflammatory properties. Use of these compounds concurrently would combine the anabolic effects of Glucosamine with the anticatabolic effects of the chondroitin sulfate. Thus these agents may act synergistically as precursor substrates, shifting the chemical equilibrium of the joint in favor of increased proteoglycan production.

## Free Radicals and Anti-Oxidants

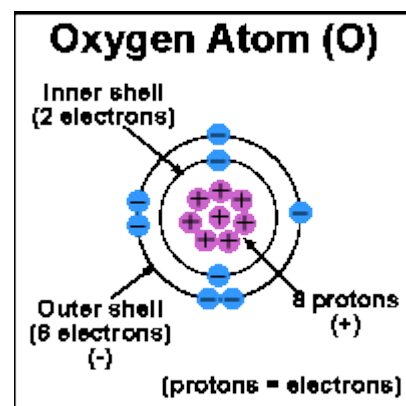
What are free radicals? Why are they damaging to the canine's body?

### **Background: A Brief Look at Chemical Bonding**

To understand the way that free radicals and antioxidants interact, you must first understand a bit about cells and molecules. The canine body is composed of many different types of cells. Cells are composed of many different types of molecules. Molecules consist of one or more atoms of one or more elements joined by chemical bonds. Atoms consist of a nucleus, neutrons, protons and electrons. The number of protons (positively charged particles) in the atom's nucleus determines the number of electrons (negatively charged particles) surrounding the atom. Electrons are involved in chemical reactions and are the substance that bonds atoms together to form molecules. Electrons surround, or "orbit" an atom in one or more shells. The innermost shell is full when it has two electrons. When the first shell is full, electrons begin to fill the second shell. When the second shell has eight electrons, it is full, and so on.

The most important structural feature of an atom for determining its chemical behavior is the number of electrons in its outer shell. A substance that has a full outer shell tends not to enter in chemical reactions (an inert substance). Because atoms seek to reach a state of maximum stability, an atom will try to fill its outer shell by:

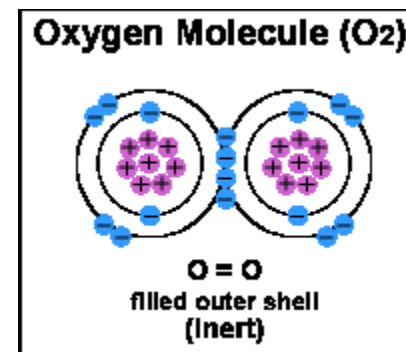
- Gaining or losing electrons to either fill or empty its outer shell
- Sharing its electrons by bonding together with other atoms in order to complete its outer shell



Atoms often complete their outer shells by sharing electrons with other atoms. By sharing electrons, the atoms are bound together and satisfy the conditions of maximum stability for the molecule.

### **How Free Radicals are Formed**

Normally, bonds don't split in a way that leaves a molecule with an odd, unpaired electron. But when weak bonds split, free radicals are formed. Free radicals are very unstable and react quickly with other compounds, trying to capture the needed electron to gain stability. Generally, free radicals attack the nearest stable molecule, "stealing" its electron. When the "attacked" molecule loses its electron, it becomes a free radical itself, beginning a chain reaction. Once the process is started, it can cascade, finally resulting in the disruption of a living cell.



Some free radicals arise normally during metabolism. Sometimes the canine's body's immune system cells purposefully create them to neutralize viruses and bacteria. However, environmental factors such as pollution, radiation, cigarette smoke and herbicides can also spawn free radicals.

Normally, the canine body can handle free radicals, but if antioxidants are unavailable, or if the free-radical production becomes excessive, damage can occur. Of particular importance is that free radical damage accumulates with age.

## **How Antioxidants May Prevent Against Free Radical Damage**

The vitamins C and E and L-Glutathione are thought to protect the body against the destructive effects of free radicals. Antioxidants neutralize free radicals by donating one of their own electrons, ending the electron-"stealing" reaction. The antioxidant nutrients themselves don't become free radicals by donating an electron because they are stable in either form. They act as scavengers, helping to prevent cell and tissue damage that could lead to cellular damage and disease.

**Vitamin E** : The most abundant fat-soluble antioxidant in the body. One of the most efficient chain-breaking antioxidants available. Primary defender against oxidation. Primary defender against lipid peroxidation (creation of unstable molecules containing more oxygen than is usual).

**Vitamin C** : The most abundant water-soluble antioxidant in the body. Acts primarily in cellular fluid. Of particular note in combating free-radical formation caused by pollution and cigarette smoke. Also helps return vitamin E to its active form.

L- Glutathione is the king of all antioxidants. It rules our body's cells, for without it, they would be helpless during the fatal onslaught of free radicals.

## **Vitamin E**

A growing body of evidence is documenting the need for protection from oxidant free-radical damage throughout life. Vitamin E has been shown to be one of the most potent biological antioxidants.

**The chief fat-soluble dietary antioxidant is Vitamin E**, which enhances cell membrane stability, enabling the exit of waste products, which often consist of free radicals.

The earliest marker of vitamin E deficiency in humans is increased hemolysis of red blood cells (RBC) on exposure to peroxide radicals. The RBC is particularly prone to lipid peroxidative damage, and vitamin E has been shown to mediate a protective effect through its antioxidant properties.

Vitamin E has also shown considerable promise for improving immunity and slowing down the progression of Alzheimer's disease. It promotes normal blood clotting, aids in preventing cataracts, maintains healthy nerves and muscles, and promotes healthy skin and hair. Vitamin E prevents cell damage by inhibiting oxidation of fats, in conjunction with selenium, and inhibiting the formation of free radicals produced by cell damage.

When an antioxidant such as vitamin E donates an electron to quench a hazardous free radical, it becomes a weak free radical itself. But vitamin E can be restored back to its full antioxidant strength when vitamin C donates an electron to it.

Vitamin E is recommended for treating pets with several disorders that may benefit from high doses of antioxidants: epilepsy, atopic dermatitis, feline leukemia, immunodeficiency and virus infections. Vitamin E is a mild antagonist to leukotriene formation. (Leukotrienes are pro-inflammatory chemicals formed from the

conversion of arachidonic acid in damaged cells' membranes.) As such, it is often used in certain immune skin disorders, including discoid lupus, erthematosus, pemphigus erthematosus, epidermolysis bullosa, and acanthosis nigricans with variable results. Vitamin E has a direct effect on the formation of dangerous blood clots. Platelets stick to the walls of blood vessels damaged by atherosclerosis, forming blood clots that can break off and cause heart attacks and strokes. Like aspirin, vitamin E interferes with the activity of blood platelets.

## **Ester- C<sup>®</sup> Calcium Ascorbate (Source of vitamin C)**

Ester-C<sup>®</sup> Chelated Mineral Blend for Animals is a patented, non-acidic form of calcium ascorbate that contains the essential minerals calcium, magnesium, manganese, and zinc bound in a pH neutral complex along with vitamin C metabolites (naturally occurring dehydroascorbate and threonate) that enhance the absorption of vitamin C. This form of ascorbate is preferred by veterinarians, as Ester-C<sup>®</sup> permits rapid absorption from the gastrointestinal tract resulting in less chance of gastrointestinal disturbances such as diarrhea. Also, Ester-C<sup>®</sup> produces higher serum levels, higher WBC levels, less oxalate excretion, and less urinary ascorbate loss than ascorbic acid.

In numerous clinical trials and studies in the U.S. and Norway, Ester-C<sup>®</sup> mineral ascorbates have been shown beneficial in alleviating signs of non-specific lameness in dogs, degenerative joint disease in horses and chronic obstructive pulmonary disease in horses. Specifically, a study done in arthritic dogs showed that 62% of dogs receiving the Chelated Mineral Blend given at a dosage of 45 mg/kg of body weight twice daily experienced improved locomotion within 5 to 8 days of usage. 44% of dogs on plain ascorbic acid at the same dosage showed some improvement, and two dogs experienced mild gastrointestinal disturbances.

Recent clinical observations indicate that the therapeutic use of vitamin C gives excellent results in the treatment of degenerative joint disease (both in humans and animals), the congestive lung disorder known as heaves in horses, and hip dysplasia and spinal disorders in dogs. At Tufts University in Boston, guinea pigs were fed a normal or high intake of vitamin C before, during and after surgery to induce knee osteoarthritis. The guinea pigs fed a standard RDA amount of vitamin C (2.4 mg daily) developed osteoarthritis, but the guinea pigs fed 150 mg of vitamin C daily developed only minor changes.

Calcium ascorbate is an acceptable ingredient (AAFCO Definition #90.25) for use as a nutritional source of vitamin C in dry (less than 13% moisture content) dog, cat and horse products.

### **Its Role in the Interrelationship of Antioxidants**

The chief water-soluble dietary antioxidant is Vitamin C, which plays numerous roles, such as quenching excess free radicals generated by the immune system and increasing glutathion production. The many antioxidants, from vitamins to endogenous enzymes, can be grouped according to their role in the prevention and reduction of oxidation reactions—with vitamins acting primarily as free radical scavengers. A free radical is a chemical species of independent existence containing one or more unpaired electrons. When this highly-reactive free radical (oxidizing agent) is rendered essentially stable by the donation of an electron (or hydrogen atom) from the antioxidant vitamin (reducing agent), the vitamin itself becomes an antioxidant radical. Vitamin C can lose one or two electrons by reaction with oxygen or oxygen radicals to form dehydroascorbate. Depending upon the relative concentrations in the aqueous phase, when glutathione acts as a scavenger, it can be regenerated by ascorbic acid. Thus if glutathione is used as a dietary component, supplemental vitamin C is considered important to maintain it in the reduced, free radical quenching form.

Ester C<sup>®</sup> (Source of Vitamin C) is required for the production of collagen, the intercellular “cement” substance that gives structure to muscles, vascular tissues, bones and cartilage. Vitamin C also contributes to the health of the teeth and gums and aids in the absorption of iron.

## **L-Glutathione**

**L-Glutathione** It is a powerful antioxidant and detoxifies the harmful compounds in the liver, where it is then excreted through the bile. The liver also excretes glutathione directly into the bloodstream where it is used to help maintain the integrity of red blood cells, as well as protecting white blood cells. Glutathione is also found in the lungs and intestinal tract where it assists in carbohydrate metabolism as well as breaking down oxidized fats. It is also used to prevent oxidative stress in most cells and helps to trap free radicals

## **SUPEROXIDE DISMUTASE**

**Superoxide Dismutase (SOD)** is a biologically active compound, and is often referred to as “the super antioxidant” because of its role in preventing free radical damage. Superoxide Dismutase belongs to a family of naturally occurring metalloenzymes that act as free oxygen radical scavengers and protect against the deleterious effects of biologically generated superoxide oxygen radicals by dismutation to hydrogen peroxide + molecular oxy. It converts the very harmful free radicals super oxide to the less active peroxide, which then can be further converted by other antioxidant enzymes into water. Free radicals are atoms with unpaired electrons, and are created through a broken bond that failed to produce ions (subatomic particles with either a positive or negative charge). Superoxide free radicals are formed during normal metabolic processes or as a reaction to toxins and infections. They can be potentially damaging because they will “steal” electrons from healthy cells and tissues.

Drugs, chemicals (insecticides), pollutants (such as ozone and cigarette smoke), some diets, normal cellular functions, and radiation are among some of the causes for the production of free radicals. Once that first free radical is produced, it will create a snowball effect to produce more free radicals unless it is stopped by the body’s antioxidant defense mechanism.

The scavenging of free radicals prevents breakdown of proteoglycans, hyaluronic acid and collagen. By protecting hyaluronate against depolymerization by free-radicals, it is indicated that exogenous SOD might have an anti-inflammatory effect. SOD exists in several forms which require three different trace elements to function correctly: copper, zinc, and manganese.

## **SOD Studies**

Animal research showed oral treatment with SOD was effective when used as an add-on therapy for treating microbial infection. Researchers noted that oral SOD suppressed the toxic side-effects of pharmaceutical therapies for visceral Leishmaniasis infection in dogs while appearing to promote the efficacy of the drugs.

Several studies in animals have also demonstrated that dietary antioxidants can definitely increase life expectancy. Antioxidant nutrients reduce the risk of cancer, heart disease, and many diseases linked to aging, including cataracts, macular degeneration and arthritis. SOD levels tend to decline with age, while free radicals production increases. SOD occurs naturally in barley grass, broccoli, brussel sprouts, cabbage, wheatgrass, and most green plants.

In human trials, SOD improved function and reduced pain in patients with osteoarthritis of the knee, slowed production of the immune protein tumor necrosis factor (partially responsible for inflammation) and stalled lactic acid buildup after exercise. It has also been shown to provide immune, neurological and cardiovascular support; to

aid lung and eye health; and to reduce toxicity of certain drug therapies that may cause tissue damage. SOD also has the abilities to go deep into muscle cell tissues where free radicals tend to accumulate.

## **Urinary Tract Support**

### **Infection Support Ingredient Descriptions**

#### **Cranberry UTS™**

Cranberry UTS™ *helps* to minimize bacterial colonization of the bladder mucosa by making the bladder lining inhospitable to bacteria. The proanthocyanidin fraction of cranberries prevents the adherence of E. coli (the bacteria responsible for most UTIs) to the wall of the urinary tract. This promotes flushing of bacteria from the bladder into the urine stream, resulting in the prevention or reduction of symptoms.

The simple sugars found in commercial cranberry juice, as well as those found in other foods, enhance bacterial growth and exacerbate the problem. To be effective, cranberry juice must be unsweetened or taken as a dry extract.

#### **Marshmallow Root**

A natural antimicrobial, demulcent, emollient, hypoglycemic and immunostimulant. It is a safe and versatile herb for animals. The mature root contains up to 35% mucilage which makes marshmallow useful for treatment of internal mucous membranes. It is particularly useful for urinary tract inflammations. In these cases, marshmallow provides a soothing, lubricating protective barrier between mucous membranes and substances which contribute to the irritation.

#### **Oregon Grape Root**

An antimicrobial herb, which contains berberine. Antibacterial properties of berberine have been shown to be effective as some forms of prescription antibiotics, including chloramphenicol when used against various forms of staphylococci. Berberine has also been shown to be active against infections of Escherichia coli (E-coli) and other gram negative-type bacteria. In the urinary tract, Oregon Grape Root is considered as an effective remedy for infections of the bladder, kidneys and urethra.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

Oregon Grape Root should not be used in animals with acute liver disease or existing liver injuries without the supervision of a veterinarian. It is safe when used properly, but will likely over-excite the liver of most animals if used excessively. Not recommended for pregnant or nursing animals.

#### **Echinacea**

Echinacea has been used to help prevent tissue damage, boost the immune system and to reduce inflammation. Many of the active components of Echinacea have antibacterial and antimicrobial properties.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

May alter P450 drugs.

## **Ester-C® Calcium Ascorbate**

(Source of Vitamin C)

Vitamin C helps make the urine acidic so it is inhospitable to bacteria. Urinary incontinence reasons can involve the bladder, the urethra, or abnormalities in the parts of the brain and spinal cord that control bladder function. Incontinence can also be confused with diseases that cause frequent urination and infections of the urine may be secondary to another cause of incontinence. A physical exam and laboratory tests are essential in the proper diagnosis to rule out submissive urination, dysuria, polyuria, neurogenic causes, ectopic ureter, urethral disease, introgenic surgical damage, territorial marking, or canine cognitive dysfunction.

## **Urethral Sphincter Mechanism Incompetence**

Urethral Sphincter Mechanism Incompetence, USMI, is the most commonly diagnosed cause of urinary incontinence: 81% of incontinent adult females and 57% of all dogs with involuntary urine loss.

The urethral sphincter smooth muscles contain receptors that can be affected by hormones (estrogen & testosterone) and incontinence in neutered animals may be due to decreased activity of these receptors. More than 20% of spayed females are affected with urinary incontinence although both male and female dogs can be affected, with medium to large breeds being more prone for the problem. The number of cases is likely to increase with the growing number of older dogs due to advances in geriatric veterinary care.

## **Estrogens**

It is not entirely clear how estrogens are helpful in the treatment of USMI. Originally, estrogens were given to post-menopausal women with urinary incontinence and the treatment was simply extrapolated to dogs. It is possible that estrogens are important in the maintenance of neuroreceptors in the bladder sphincter and without estrogens the receptors become unresponsive to the transmission of the “storage” message from higher neurologic centers. In dogs, DES (diethylstilbestrol) is the most common estrogen used, though it is now only available through [compounding pharmacies](#). In male dogs, testosterone seems to be more effective than estrogens, possibly through action on the prostate which sits at the neck of the bladder and incorporates the sphincter. During the 1960s DES was used as a growth hormone in the beef and poultry industry. It was later found to cause cancer and was phased out in the late 1970s.

In humans, researchers are still uncovering facts about the life-long effect of exposure to DES, including higher rates of breast cancer in DES mothers, reproductive abnormalities in daughters and sons, higher rates of ectopic pregnancy in daughters, and damage to the endocrine and immune systems. No substantial research sources could be found on the long term DES effects in canines.

## **Alpha-Adrenergic Agonists**

These medications act by enhancing release of the neurotransmitter chemicals that act on the receptors of bladder sphincter. Effectively, they turn up the volume dial on the “hold it” message from the high neurologic areas. The usual medication for canine use is [phenylpropanolamine](#), or PPA. On December 22, 2005 the FDA issued a proposed rulemaking notice for products containing phenylpropanolamine preparations. This proposed rule reclassifies phenylpropanolamine as nonmonograph, category II, not generally recognized as safe and effective.

Back in 1996 the FDA proposed additional warning labels on products containing PPA for humans. Their findings revealed PPA affects the central nervous system and the cardiovascular system and should not be taken with other products that contain phenylephrine, pseudoephedrine or ephedrine, which have similar effects on the body. PPA also interacts with certain antidepressants known as monoamine oxidase inhibitors (MAOI), which when combined with PPA can cause life-threatening adverse effects. In addition, persons with high blood pressure, heart or thyroid disease, or diabetes were advised not to use PPA without consulting a doctor.

At this time most dogs, male and female alike, are believed to tolerate phenylpropanolamine uneventfully.

### **Anticholinergics**

Anticholinergic drugs are medications that work, not on the sphincter of the bladder, but on the rest of the bladder where urine is stored, relaxing the muscle fibers thus facilitating storage. An example of such drug would be imipramine, an anti-anxiety medication commonly used in humans. It has anticholinergic properties that have been used in combination with PPA in the treatment of animal incontinence.

Drug therapy for incontinence may be based on "trial" of different drugs in various doses. Since some of these drugs can have side effects low doses are tried first. Some drugs may be slow to have an effect so as long as there are no undesirable side effects, a drug trial often continues for several weeks before the drug is considered not to be effective.

### **Alternatives to PPA or DES**

Once the incontinence diagnosis due to endocrine imbalance is made, the benefits of phytoestrogen supplementation may be explored. While bone marrow suppression and a higher incidence of mammary neoplasias have been linked to DES usage in humans, to this date, no published research has proven similar problems with the phyto-estrogenic precursors present in Chinese Wild Yam, Bee Pollen, Chinese Angelica or Chinese Foxglove (Rehmannia).

### **Phytoestrogens**

Most common phytoestrogens are found in plants. Their name comes from *phyto* = plant and *estrogen* = estrus (period of fertility for female mammals) + *gen* = to generate. Phytoestrogens, sometimes called "dietary estrogens", are a diverse group of naturally occurring non steroidal plant compounds structurally similar to [estradiol](#). Estradiol, 17 $\beta$ -estradiol, is a [sex hormone](#) derived from [cholesterol](#). After [side chain](#) cleavage and utilizing the delta-5 pathway or the delta-4 pathway androstenedione is the key intermediary. A fraction of the androstenedione is converted to testosterone, which in turn undergoes conversion to estradiol by an enzyme called aromatase.

Alternatively, androstenedione is "aromatized" to estrone, which is subsequently converted to estradiol, and has the ability to cause estrogenic or/and antiestrogenic effects.

The similarities, at molecular level, of [estrogens](#) and phytoestrogens allow them to mildly mimic and sometimes act as antagonists to [estrogen](#). Phytoestrogens were first observed in 1926<sup>[1][2]</sup> but it was unknown if they could have any effect in human or animal metabolism. In the 1940s it was noticed for the first time that [red clover](#) (a phytoestrogens-rich plant) pastures had effects on the fertility of grazing sheep.

In addition to interaction with estrogen receptors, phytoestrogens may also modulate the concentration of endogenous estrogens by binding or inactivating some enzymes and may affect the bioavailability of sex hormones by binding or stimulating the synthesis of sex hormone binding globuline (SHBG). Phytoestrogens are considered archiestrogens (ancient, naturally occurring) and as dietary phytochemicals they are considered as co-evolutive with mammals. When using natural supplements (phytoestrogens) to provide nutritional support to dogs stressed by disease or dysfunction, you should allow 4-6 weeks for nutrient levels to balance in cellular structures.

## **INGREDIENT DESCRIPTIONS**

### **Rehmannia**

Rehmannia root powder has been used to enhance [energy](#). Rehmannia is involved in red blood cell regeneration and brings blood to the kidneys and replenishes the vital essence. Rehmannia contains the vitamins A, B, C, and D, as well as other useful compounds.

The root is native to China, Japan, and Korea. Traditionally Rehmannia root has been used to replenish vitality, strengthen the [liver](#), kidney, and heart, and for treatment of a variety of ailments like diabetes, anemia, and urinary tract problems. This herb has fatty acids, palmitic acid, beta-sitosterol, daucosterol and sulfur cyclic compounds, along with rehmapicroside, norcarotenoids, 2-formyl-5-hydroxy-methylfurane, the iridoid rehmaglutin D, iridoid glycosides, and phenylethyl alcohol glycosides. The dried root is also used to treat bleeding due to blood deficiency and to nourish the vital essence

#### **SAFETY PRECAUTIONS AND INTERACTIONS**

Can cause diarrhea, loss of appetite or upset stomach. Not recommended for pregnant or nursing animals. May cause bilirubin and creatinine values outside normal limits. No toxicology well documented.

### **Wild Yam Root:**

Has a diuretic effect, and combined with its antispasmodic action, soothes painful conditions of the urinary tract. It is also a phyto-estrogenic precursor and contains natural estrogen.

#### **SAFETY PRECAUTIONS AND INTERACTIONS**

Not recommended for pregnant or nursing animals.

#### **SAFETY PRECAUTIONS AND INTERACTIONS**

In rare cases, may cause an upset stomach.

### **Dang Gui Shen:**

An effective blood tonic which strengthens organ functions. It is a phytoestrogenic precursor.

### **Licorice:**

Harmonizes the other herbal ingredients in the formula and affects the body's endocrine system as it contains isoflavones (phytoestrogens). It is also a smooth muscle anti-spasmodic. **Licorice has anti-inflammatory and anti-viral properties, and** contains high levels of flavonoids and antioxidants that work to protect the body against effects of aging. Licorice is often recommended to improve adrenal function.

#### **SAFETY PRECAUTIONS AND INTERACTIONS**

Not recommended for pregnant or nursing animals. Overdose may cause hypokalemia. Caution is advised for animals with pre-existing cardiovascular conditions. Licorice may elevate blood sugar levels in diabetic animals.

### **Oregon Grape Root**

An antimicrobial herb, which contains berberine. Antibacterial properties of berberine have been shown to be as effective as some forms of prescription antibiotics, including chloramphenicol when used against various forms of staphylococci. Berberine has also been shown to be active against infections of Escherichia coli (E-coli) and other

gram negative-type bacteria. In the urinary tract, Oregon Grape Root is considered an effective remedy for infections of the bladder, kidneys and urethra.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

Oregon Grape Root should not be used in animals with acute liver disease or existing liver injuries without the supervision of a veterinarian. It is safe when used properly, but will likely over-excite the liver of most animals if used excessively. Berberine may inhibit vitamin B assimilation. It is not recommended for nursing or pregnant animals.

### **Marshmallow Root**

A natural antimicrobial, demulcent, emollient, hypoglycemic and an immunostimulant. It is a safe and versatile herb for animals. The mature root contains up to 35% mucilage which makes marshmallow useful for treatment of internal mucous membranes. It is particularly useful for urinary tract inflammations. In these cases, marshmallow provides a soothing, lubricating protective barrier between mucous membranes and substances which contribute to the irritation.

Marshmallow has long been used as a food plant and its safety is substantiated by many years of use in both humans and animals.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

Marshmallow root has been known to lower blood sugar levels, and therefore should be used with caution in hypoglycemic animals. It may also retard the intestinal absorption of some drugs.

### **Urinary Comfort™**

Urinary Comfort™ helps to minimize bacterial colonization of the bladder mucosa by making the bladder lining inhospitable to bacteria. The proanthocyanidin fraction of cranberries prevents the adherence of E. coli (the bacteria responsible for most UTIs) to the wall of the urinary tract. This promotes flushing of bacteria from the bladder into the urine stream, resulting in the prevention or reduction of symptoms.

The simple sugars found in commercial cranberry juice, as well as those found in other foods, enhance bacterial growth and exacerbate the problem. To be effective, cranberries must be unsweetened or taken as a dry extract. Urinary Comfort™ **does not** contain any sugars.

### **Ascorbic Acid (Vitamin C)**

Vitamin C helps make the urine acidic so it is inhospitable to bacteria. Vitamin C has non nutritional properties in higher dosages. For example, the anti inflammatory and antioxidant properties of large doses of Vitamin C are widely recognized.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

Vitamin C may also reduce the blood-thinning effects of Coumadin (warfarin) and Heparin. It may increase the blood levels of some drugs, such as aspirin and other salicylates.

### **Alfalfa**

Alfalfa is high in protein, calcium, other minerals, vitamin A, and vitamins in the B group, vitamin C, D, E and vitamin K. It is used to treat disorders related to the digestive tract and the kidneys. Alfalfa can also be used as an [estrogen](#) replacement. It is widely used in homeopathic medicines worldwide. Today, alfalfa is suggested for treating [anemia](#), [diabetes](#), to extend [appetite](#) and contribute towards [weight](#) gain, as a [diuretic](#) for increased [urination](#), for [indigestion](#) and [bladder disorders](#).

## **All Natural Ear Wash**

The formula below is gentle, yet effective, and designed to help dissolve earwax and remove foreign debris. It can be used as often as needed and is especially recommended after bathing or swimming. This formula contains Tea Tree Oil, which acts as a natural disinfectant, killing fungus and bacteria, including some resistant to some powerful antibiotics.

It is recommended the ear wash pH be 3.5-4.0.

### **Ingredient Descriptions**

#### **Witch Hazel**

Witch Hazel is a natural astringent, anti-inflammatory and hemostatic. It is derived from *Hamamelis virginiana*. The medicinal parts are the plant's hamamelis water, which is distilled from various plant parts: the bark, the fresh and dried leaves, the fresh bark of the roots and branches, and the dried bark of the trunk and branches. Usage approved by Commission E: Inflammation of the skin, wounds and burns.

#### **Glycerine**

Emollient, demulcent. Used as a humectant, lubricant and softener to help loosen ear wax.

#### **Boric Acid**

Used as an astringent and antiseptic. It is antibacterial and antifungal, and has been found to lower the pH.

#### **Tea Tree Oil**

The terpenes present in this essential oil exhibit efficacy that is antimicrobial, possibly antiviral and weakly antimycotic. Good for disinfecting wounds and healing virtually all skin and fungal infections. Derived from the branch tips and leaves of the *Melaleuca alternifolia* which is indigenous to Australia. The oil is extracted by steam distillation.

The percentage of Tea Tree Oil is only 0.3% of the formula, making it safe for cats in this product.

#### **Echinacea Extract**

Effects are: Immunostimulating, anti-inflammatory, cytokine stimulation and collagen protectant. It can be derived from the whole plant.

### **How a dog's ear works**

A dog has such keen hearing that they can tell the difference in the footsteps of each family member. Dogs can hear the high pitched squeak of a burrowing rodent and other prey.

## **How a dog's ear works cont.**

Your dog's ears also help them maintain balance, similar to the way human ears work, only on a much finer scale. A dog ear has tiny hairs that are filled with fluid and crystals that help detect the slightest change in the position of the dog's head. This allows the animal to move its head, as needed, to best direct sounds down its auditory canal.

The dog's auditory canal is a passageway that begins at the ear and extends inward and downward, it is lined with skin and hairs and is approximately 2 inches long. This inward and downward angle has a rather sharp 90 degree turn and this is where the most junk or what we call ear jam gathers. On the other hand, The human's auditory canal is a passageway that begins at the ear and extends inward and slightly upward, it is lined with skin and hairs and is approximately 1 inch long. The downward slope allows ear wax to slide out most likely ending up on your pillow at night.

The outer one-third of the dog's ear canal is lined with wax-producing cells and fine hairs. The purpose of the ear wax and hairs is to protect the eardrum (which lies at the end of the canal) by trapping dirt and foreign bodies and keeping the canal moist. Cleaning of the ear canal usually occurs naturally as a result of the "conveyor belt" process of migration, aided by jaw movement. Cells formed in the ear migrate outward to the walls of the ear canal, and accelerate towards the entrance of the ear canal; this process occurs at a rate equivalent to that of toenail growth.

The wax slowly works its way to the outside, taking the trapped dirt and dust with it. In other words, earwax is good!

Wax and debris clogs are most likely to occur at the rather sharp angle of the dogs ear canal. So what's the problem? Compared to humans, your dog's ear canal has a rather sharp angle in it; this is where most debris gets plugged and is the origin of many ear infections. There are a number of common culprits including bacteria, yeasts and mites. Less commonly, allergies may have a role to play in inflammation and subsequent infection of the ears. Ear infections are very common amongst dogs and can cause severe irritation and discomfort to your dog.

Common signs of ear infection are:

- Shaking of the head and ears
- Scratching or rubbing the ears & face
- Discharge or bleeding from the ears
- Foul smell coming from the ears
- Sensitivity to touching in the ear area
- General irritability

Natural remedies can treat and prevent infections of the ear without any of the side-effects or adverse effects on immune function that antibiotics may cause.

Too often, ear wash cleaners for dogs contain large amounts of alcohol with the idea that the alcohol will kill bacteria, mites and yeasts. The problem is, even if it does, there can be secondary damage caused by the alcohol. Also, alcohol poured over an open wound or sore can cause a great amount of pain and stinging, leading to drying and flaking of the inner ear and extreme discomfort for your dog.

Ear Wash with Tea Tree Oil and Witch Hazel contains a blend of natural, herbal ingredients, all specially selected to treat and prevent ear infections and ear mites without the side effects of prescription drugs or the health and environmental risks associated with commercial synthetic pesticides. It can provide safe, yet effective, relief from your pet's ear problems, and helps to prevent the spread of mites from one pet to another. It also naturally soothes and deodorizes, gently aids in dissolving ear wax, removes foreign debris, and helps disinfect the ear canal, which prevents the re-occurrence of ear problems.

## **Digestive Enzymes & Probiotics**

So much discussion is given to Probiotics which are mainly found in the lower bowels but certainly just as important are the Enzymes found upstream in the stomach and small intestine. Both are organic catalysts that affect the rate at which chemical reactions occur for specific substrates, including food. Enzymes are proteins made up of amino acids or their derivatives, which catalyze a defined chemical reaction. There are four main categories of digestive enzymes: amylase, protease, cellulase and lipase. Amylase breaks down carbohydrates, protease helps digest protein, cellulase breaks down fiber or cellulose and lipase aids in the digestion of fats.

These digestive enzymes are naturally produced by your dog but not in nearly the quantity needed to digest most of today's commercial dog foods which contain even higher amounts of protein, fats and fiber. It is my opinion that the "race" to see who can add the most protein, fat and fiber to commercial dog food may actually be a cause of what is being diagnosed as food allergies.

Your dog needs enzymes and bacteria to digest food and in the past some of these enzymes could be found in the food itself. Unfortunately, many natural enzymes and bacteria found in today's dog food ingredients are killed during the manufacturing process. Without these necessary elements, the nutrients needed to keep your dog's skin, organs and coat healthy may be missing, once again adding to the symptoms diagnosed as food allergies.

### **The Role of (Upstream) Digestive Enzymes**

Digestive enzymes and an assortment of beneficial bacteria and yeast (probiotics) are needed to break down and transport food nutrients in the body. Killed at temperatures above 118° to 170°, digestive enzymes are not available in commercial dog foods. The results can be catastrophic, without sufficient enzymes present in the stomach and small intestine (upstream), the dog's ability to break down proteins, fats, carbohydrates, and fiber are greatly reduced leaving foodstuffs to enter into the large intestine (downstream) in a form not easily broken down by the bacterial probiotics. The results is poor digestion, poor absorption and poor nutrition.

Enzymes are catalysts, which mean they cause an internal action without themselves being destroyed or changed in the process. Each digestive enzyme acts on a specific food component and one cannot be substituted for another. In the absence of these nutritional workhorses, the body's ability to utilize the food it receives is greatly diminished. A good enzyme supplement maximizes the nutritional value of any diet by optimizing digestion and the absorption of nutrients. The more enzymes which are in the foods our pets eat, the less digestive work must be done by their digestive organs. Enzymes work synergistically with the coenzymes: vitamins and minerals and consequently these coenzymes do not work without enzymes and vice versa. If we are feeding an enzyme-free diet, while also sprinkling a vitamin/mineral supplement over these foods, the added supplements may be of little value unless sufficient enzymes are present in the diet and/or are produced by the body.

Food enzymes do a portion of this laborious job of pre-digestion, thereby leaving the pet's body a sufficient supply of metabolic enzymes to draw on for maintaining and strengthening the many other bodily systems. As a result, the immune system, digestive system, hormonal glands and organs are in their optimum working order. The late Dr. Edward Howell, a physician and pioneer in enzyme research, called enzymes the "sparks of life." These energized protein molecules play a necessary role in virtually all of the biochemical activities that go on in the body. Digestive enzymes are secreted along the gastrointestinal tract and break down foods, enabling the nutrients to be absorbed into the bloodstream for use in various bodily functions. There seems to be a finite reservoir of enzymes in the body. If various organs and glands are continually robbed of their own enzymes, which must be utilized to digest food, then eventually the body breaks down. Taking enzyme supplements helps prevent depletion of the body's own enzymes and thus reduces the stress on the body.

## **Veterinarian Recommended Digestive Enzymes**

There are three main categories of digestive enzymes: amylase, protease, and lipase. Amylase breaks down carbohydrates, protease helps digest protein, and lipase aids in the digestion of fats. Dogs and cats do not normally have the enzyme cellulase in their bodies, and that's why they can only digest some of the plant material in their diets. Supplementation with digestive enzyme products that contain cellulase seems to be more advantageous to pets with medical problems as it liberates chemicals such as zinc, selenium, and linoleic acid that might be bound by fiber. In one study, supplementing the diet with additional zinc did not confer the same benefits, improved growth and efficiency, as supplementing with plant enzymes. Zinc can protect against cellular damage caused by the tumor necrosis factor.

## **Plant Enzyme Sources versus Animal Enzyme Sources**

Dr. Edward Howell, the enzyme pioneer, developed supplements derived from *aspergillus oryzae* (a fungus) after finding them to be more effective than animal-based pancreatic supplements. Subsequent research has confirmed his original conclusions. A comprehensive article on digestive enzymes in the August 1993 issue of *The Townsend Letter For Doctors*, cited the following scientific findings: *Aspergillus* enzymes possess unusually high stability and activity under a wide range of pH conditions, distinguishing them from animal enzymes (i.e., pepsin, pancreatin, trypsin, chymotrypsin, pancrelipase and pancreatic amylase), which require pH conditions often lacking when impaired health is involved. Protease from *aspergillus*, absorbed into the bloodstream, may be able to hydrolyze dietary proteins and polypeptides, which have leaked into the bloodstream as food antigens. Such substances absorbed intact from the gut can cause disturbances in the body. A 1998 study in England with dogs found that a small dose of *aspergillus* lipase was as effective as conventional pancreatin 25 times larger in the treatment of malabsorption, malnutrition and steatorrhea due to pancreatic insufficiency.

The plant enzymes are active over a much wider pH range (pH 3 to 9) than pancreatic enzymes and are the preferred enzymes for most patients.

## **The Effect on Health and Disease**

An improper diet and damaging environmental factors could affect the efficiency of internal enzyme function and reduced digestive competency. Cooked foods and dry convenient diets have been denatured and are devoid of enzymes. Internal enzymes are damaged by factors such as chlorine in drinking water, certain medicines, air pollution, and chemical additives. Supplying additional enzymes, through the use of supplementation, can replenish enzymes absent in processed foods and supports digestive work that must be done by the digestive organs. Additionally, various stressors such as illness, anxiety, allergies, food intolerance, age, and various orally administered medications can decrease gastrointestinal function. This results in poor digestion and absorption of the nutrients in the diet. Unassimilated proteins, carbohydrates, fats, as well as bacterial, viral, and yeast cells can be reabsorbed into the bloodstream from the digestive tract, and may cause allergies, skin diseases, and other illness. These antigens or toxins induce the immune system into action to create antibodies as a defense. Toxins that are absorbed into the bloodstream can be deposited at body sites other than the intestinal tract. After eating a denatured meal when digestive enzymes are needed, the WBC increases, seemingly to aid in the digestive process. This is termed "Digestive Leukocytosis" and occurs roughly 30 minutes after eating a cooked meal, stressing the immune system.

## **The Effect on Health and Disease cont.**

Cellular pathologist, Rudolph Virchow first reported the concept of the immune system being stimulated every time we eat in 1897. If food sits in the digestive tract too long it rapidly builds up toxins and then weakens the body and leaves it vulnerable to disease and infection. This increases the WBC count and jeopardizes the immune system

function. Enzymes have as much importance in our pet's diet as any other element of nutrition. Degenerative diseases and cancer in particular, have been linked to enzyme deficiencies by researchers from the Universities of London, Wales, Wisconsin, Loyola and Yale Medical School. Michael Lemmon, DVM, at his Highlands Veterinary Clinic in Renton, WA. believes enzymes are a primary tool in dealing with many different problems. In Lemmon's experience, the enzymes may also aid older animals suffering from joint ailments. By enhancing digestion and absorption of nutrients, including anti-oxidants and the mineral magnesium, the body is better able to counteract harmful degenerative processes. Deficiencies can also be genetically related and symptoms will show up among kittens and puppies.

## **Probiotics**

Probiotics are defined as normal viable bacteria residing in the intestinal tract that promote normal bowel health. Probiotics are given orally and are usually indicated for use in intestinal disorders in which specific factors can disrupt the normal bacterial population, making the pet more susceptible to disease.

Specific factors that can disrupt the normal flora of the bowel include surgery, medication (including steroids and non-steroidal anti-inflammatory drugs), antibiotics (especially when used long-term), shipping, birthing, stress, weaning, illness such as parvovirus infection and poor dietary factors.

Improving the nutritional status of the intestinal tract may reduce bacterial movement across the bowel mucosa, intestinal permeability, and systemic endotoxemia. In addition, probiotics may allow for better conversion of food into nutrients. The intestinal tract, especially the large intestine is home to millions of bacteria, most of which are beneficial to the pet. The intestinal bacteria are essential to digestion and the synthesis of vitamin K and many of the B vitamins.

Probiotics produce inhibitory chemicals that reduce the numbers of harmful bacteria and possibly toxin production by these harmful bacteria; probiotics may block the adhesion of harmful bacteria to intestinal cells; probiotics may compete for nutrients needed for growth and reproduction by harmful bacteria; or probiotics may degrade toxin receptors located on intestinal cells, preventing toxin absorption and damage by toxins produced by harmful intestinal bacteria. Supplementing with probiotics may also stimulate immune function of the intestinal tract. Antibiotics can disturb the balance of the intestinal tract by killing friendly bacteria. When this happens, harmful bacteria and yeasts can move in, reproduce, and take over. Probiotics are living creatures, not chemicals, so they can sustain themselves in the body unless something comes along to damage them, such as antibiotics. Dosages of probiotics are expressed not in grams or milligrams, but in millions of organisms. The suggested dosage range of probiotics for pets is approximately 20 to 500 million microorganisms.

## **Fatty Acids**

In chemistry, especially biochemistry, a fatty acid is a carboxylic acid often with a long unbranched aliphatic tail (chain), which is either saturated or unsaturated. Carboxylic acids as short as butyric acid (4 carbon atoms) are considered to be fatty acids, while fatty acids derived from natural fats and oils may be assumed to have at least 8 carbon atoms, e.g. caprylic acid (octanoic acid). Most of the natural fatty acids have an even number of carbon atoms, because their biosynthesis involves acetyl-CoA, a coenzyme carrying a two-carbon-atom group.

### **Essential Fatty Acids Overview**

EFAs are fatty acids that cannot be constructed within an organism from other components by any known chemical pathways, and therefore must be obtained from the diet. The term refers to those involved in biological processes, and not fatty acids which may just play a role as fuel. It is possible they can be underestimated as organisms and can still survive in malnourished conditions.

By playing a part in many metabolic processes, there is evidence to suggest that low levels of essential fatty acids, or the wrong balance of types among the essential fatty acids, may be a factor in a number of illnesses, including osteoporosis. Between 1930 and 1950, arachidonic acid and linolenic acid were termed 'essential' because each was more or less able to meet the growth requirements of rats given fat-free diets. To some extent, any  $\omega$ -3 and any  $\omega$ -6 can relieve the worst symptoms of fatty acid deficiency. Particular fatty acids are still needed at critical life stages (e.g. lactation) and in some disease states. In nonscientific writing, common usage is that the term *essential fatty acid* comprises all the  $\omega$ -3 or  $\omega$ -6. Authoritative sources include the whole families, without qualification.

There are two families of EFAs:  $\omega$ -3 (or omega-3 or n-3) and  $\omega$ -6 (omega-6, n-6.) Fats from each of these families are essential, as the body can convert one omega-3 to another omega-3, for example, but cannot create an omega-3 from scratch. They were originally designated as **Vitamin F** when discovered as essential nutrients in 1923. In 1930, work by Burr, Burr and Miller showed that they are better classified with the fats than with the vitamins. Mary Enig, PhD, has pointed out numerous studies showing the need for omega-3 and omega-6 essential fatty acids in mammals.

Cats lack an adequate liver capacity to synthesize the longer-chain omega (n-6 and n-3) polyunsaturated fatty acids (LCPUFAs) that, upon release into the blood, are incorporated into membrane phospholipids in many tissues and serve essential structural and signaling functions. The necessity and importance of a dietary source of the n-3 LCPUFA docosahexaenoic acid (DHA) has prompted an evaluation of the effects of supplementation of a typical cat diet with a DHA-enriched salmon oil, on the n-3 LCPUFAs in plasma, and the relative levels of n-6 and n-3 LCPUFAs. Supplementation resulted in rapid increases in both DHA and eicosapentaenoic acid (EPA) in total plasma fatty acids and in plasma phospholipids. These changes produced shifts in the overall n-6:n-3 ratio present in plasma fatty acids while markedly shifting the relative levels of arachidonic acid (AA) to DHA (AA:DHA) and arachidonic acid to EPA (AA:EPA) ratios to substantially lower values and a more favorable balance. The importance of providing DHA and EPA to the cat was reviewed and the potential benefits discussed.

### **Balance**

The biological effects of the  $\omega$ -3 and  $\omega$ -6 fatty acids are mediated by their mutual interactions. Research shows that most commercial pet food contains more than the required amount of linoleic acid, however, it is not the amount, but the ratio of Omega-6 to Omega 3 fatty acids that is most beneficial to dogs and cats. Per Dr. Campbell, both Omega-6 and Omega-3 fatty acids are important for allergic pets. "Omega-6 fatty acids keep the skin hydrated and help create a protective barrier against absorbing allergens, while Omega-3 fatty acids can minimize inflammation caused by allergens."

## **Balance cont.**

In the body, essential fatty acids serve multiple functions. In each of these, the balance between dietary  $\omega$ -3 and  $\omega$ -6 strongly affects function. They are modified to make:

The classic eicosanoids, affecting inflammation and many other cellular functions.

The endocannabinoids, affecting mood, behavior and inflammation.

The lipoxins from  $\omega$ -6 EFAs and resolvins from  $\omega$ -3, in the presence of aspirin, down regulate inflammation, and

The isofurans, neurofurans, isoprostanes, hexoxilins, epoxyeicosatrienoic acids (EETs) and Neuroprotectin D.

They form lipid rafts, affecting cellular signaling, and act on DNA, activating or inhibiting transcription factors such as NF $\kappa$ B, which is linked to pro-inflammatory cytokine production.

It should be stressed that certain components of the diet actually reduce (but do not eliminate) requirements for EFAs. The main one is saturated fatty acids which help us conserve EFAs and put them in the tissues where they belong. Some studies indicate that vitamin B6 can ameliorate the problems caused by EFA deficiency, possibly by helping us use them more efficiently. Many Omega supplements contain vitamins B and or E, which helps certain species utilize fatty acids better.

## **Omegas Role In Arthritis**

Phospholipids are found in joint cell membranes. When the membrane is injured, an enzyme acts on the phospholipids to produce fatty acids including arachidonic acid, an omega 6 fatty acid, and eicosapentaenoic acid, an omega 3 fatty acid. With further metabolism of the arachidonic acid and eicosapentaenoic acid by additional enzymes, the lipoxygenase and cyclooxygenase pathways, produce chemicals called eicosanoids.

There are four families of eicosanoids—the prostaglandins, prostacyclins, the thromboxanes and the leukotrienes. For each, there are two or three separate series, derived either from an  $\omega$ -3 or  $\omega$ -6 essential fatty acid. These series' different activities largely explain the health effects of  $\omega$ -3 and  $\omega$ -6 fats. The eicosanoids produced by metabolism of arachidonic acid are pro-inflammatory, suppress the immune system, and cause platelets to aggregate and clot. Overproduction of the eicosanoids are responsible for producing inflammation, including arthritis. The eicosanoids produced by metabolism of eicosapentaenoic acid are non-inflammatory.

In general, the products of omega 3, specifically EPA, and one omega 6 fatty acid, DGLA, are less inflammatory than the products of arachidonic acid, another omega 6 fatty acid. By changing dietary fatty acid consumption, the eicosanoid production changes right at the cellular level, decreasing inflammation within the body. Often fatty acids are added to the diet with other supplements to attain an additive effect. This is especially common in arthritic dogs, as fatty acid supplements by themselves usually fail to relieve pain and lameness.

## **Omega 3**

**$\omega$ -3 fatty acids** are a family of polyunsaturated fatty acids which have in common a carbon-carbon double bond in the  $\omega$ -3 position.

Important nutritionally essential  $\omega$ -3 fatty acids are:  $\alpha$ -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Flax and its oil are perhaps the most widely available botanical source of  $\omega$ -3. Flaxseed oil consists of ca. 55% ALA (alpha-linolenic acid). Flax contains approximately three times as much  $\omega$ -3

## **Omega 3 cont.**

as  $\omega$ -6. 15 grams of flaxseed oil provides ca. 8 grams of ALA, which is converted in the body to EPA and then DHA at efficiency of 2%-15% respectively.

### **$\alpha$ -Linolenic acid**

ALA is an isomer, compounds with the same [molecular formula](#) but different [structural formula](#), of  [\$\gamma\$ -linolenic acid](#), a polyunsaturated [n-6](#) (omega-6) fatty acid. Synthesis of the longer  $\omega$ -3 fatty acids from linolenic acid within the body is competitively slowed by the  $\omega$ 6 analogues. Linolenic acid also acts as an anti-inflammatory agent by stimulating the production of certain hormone-like substance prostaglandins. Thus accumulation of long-chain  $\omega$ -3 fatty acids in tissues is more effective when they are obtained directly from food or supplementation, or when competing amounts of  $\omega$ 6 analogs do not greatly exceed the amounts of  $\omega$ -3.

Seed oils are the richest sources of ALA, notably those of [rapeseed \(canola\)](#), [soybeans](#), [walnuts](#), [flaxseed](#) (Linseed), [perilla](#), [chia](#) and [hemp](#). ALA is also obtained from the [thylakoid membranes](#) of the green leaves of broadleaf plants (the membranes responsible for photosynthesis). Greens, therefore, and animals that eat greens, are often a good source of ALA.

### **Docosahexaenoic acid**

Commonly known as **DHA**, it is an [omega-3 essential fatty acid](#). In chemical structure, DHA is a [carboxylic acid](#) with a 22-carbon chain and six [cis](#) double bonds; the first double bond is located at the third carbon from the omega end.

DHA is most often found in [fish oil](#). Most of the DHA in fish and other more complex organisms originates in various photosynthetic and heterotrophic microalgae, and concentrates in organisms as it moves up the food chain. DHA is also commercially manufactured from microalgae. Most animals make very little DHA through metabolism; however small amounts are manufactured internally through the consumption of  [\$\alpha\$ -linolenic acid](#), an omega-3 fatty acid found in [chia](#), [flax](#), and many other seeds and nuts.

DHA is metabolized to form the [docosanoids](#)—several families of potent hormones. DHA is a major fatty acid in sperm and brain [phospholipids](#), and especially in the retina. Of all the fatty acids, DHA has the largest effect on brain PUFA composition, comprising 40% of the PUFAs in the brain. 50% of the weight of the [neuron's plasma membrane](#) is composed of DHA. It also comprises 60% of the PUFAs in the retina.

DHA is found in three [phospholipids](#): [phosphatidylethanolamine](#), [ethanolamine plasmalogens](#), and [phosphatidylserine](#) (PS). It modulates the carrier-mediated transport of choline, glycine, and taurine, the function of delayed rectifier [potassium channels](#), and the response of [rhodopsin](#) contained in the [synaptic vesicles](#), among many other functions

In humans, dietary DHA may reduce the risk of [heart disease](#) by reducing the level of [blood triglycerides](#). Low levels of DHA result in reduction of brain [serotonin](#) levels and lower neural cell PS increase neural cell death.

### **Eicosapentaenoic acid**

EPA, is another [omega-3 fatty acid](#). In physiological literature, it is given the name 20:5(n-3). It also has the trivial name [timnodonic acid](#). In chemical structure, EPA is a [carboxylic acid](#) with a 20-[carbon](#) chain and five [cis](#) double bonds; the first double bond is located at the third carbon from the omega end.

EPA and its [metabolites](#) act in the body largely by their interactions with the metabolites of [arachidonic acid](#). EPA is a [polyunsaturated fatty acid](#) that acts as a precursor for [prostaglandin-3](#), which inhibits [platelet](#) aggregation, [thromboxane-3](#), and [leukotriene-5](#) groups. all [eicosanoids](#). It is obtained in the diet by [eating oily fish](#) or [fish oil](#)—[cod liver](#), [herring](#), [mackerel](#), [salmon](#), [menhaden](#) and [sardine](#). The US [National Institute of Health's](#) MedlinePlus lists a large number of conditions in which EPA, alone or in concert with other  $\omega$ -3 sources, is known or thought to be effective. Most of these involve its ability to lower [inflammation](#).

## **Omega 3 cont.**

Karen Campbell, veterinary dermatologist, University of Illinois, states “The Metabolic process prefers omega-3 fatty acids, so the body will use them first to product the less inflammatory eicosanoids.” Omega-3 fatty acids are found in fish and flaxseed oils. Since these foods are less common in diets than corn or soy, most animals typically consume lower amounts of Omega-3 fatty acids. Supplementation can help provide these oils, which may also be essential for brain development in young animals.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

EPA has inhibitory effect on CYP2C9 and CYP2C19 hepatic enzymes. At high dose, it may also inhibit the activity of CYP2D6 and CYP3A4, important enzymes involved in drug metabolism.

## **Omega 6**

**$\omega$ -6 fatty acids, omega-6 fatty acids**, are a family of polyunsaturated fatty acids which have in common a carbon-carbon double bond in the  $\omega$ -6 position; that is, the sixth carbon from the end of the fatty acid. They include gamma-linolenic acid or **GLA**, dihomo-gamma-linolenic acid or **DGLA**, and arachidonic acid or **AA**. Dietary sources of  $\omega$ -6 fatty acids include: nuts, cereals, whole -grain breads, most vegetables oils, eggs, and poultry. Omega-6 fatty acids are essential for maintenance of skin and coat condition, normal growth, proper membrane structure, and the absorption of fat-soluble vitamins.

$\omega$ -6 fatty acids constitute our cell membranes. During assorted biochemical situations, it becomes necessary to produce prostaglandins and leukotrienes. These substances are made from  $\omega$ -6 fatty acids and the prostaglandins and leukotrienes often resulting in itching and inflammation; leading to clinical skin problems. The biological effects of the  $\omega$ -6 fatty acids are largely mediated by their interactions with the  $\omega$ -3 fatty acids. Linoleic acid, the shortest chain  $\omega$ -6 fatty acid, is an essential fatty acid. The COX-1 and COX-2 inhibitor medications, used to treat inflammation and pain, work by preventing the COX enzymes from turning arachidonic acid into inflammatory compounds.<sup>[4]</sup> (See Cyclooxygenase for more information.) The LOX inhibitor medications work by preventing the LOX enzyme from converting arachidonic acid into the leukotrienes.

### **Gamma-linolenic acid**

**GLA** is found in evening primrose and borage oils. The **GLA** oils are especially useful with arthritis, diabetes and skin disorders. Only the omega-6's can convert themselves into **GLA**.

Though some have argued that **GLA** competes with omega-3 fatty acids and renders them less effective, in reality they are synergistic. Most practitioners who endorse essential fats recommend both omega-3s and **GLA**, giving the body all the raw materials to make what eicosanoids it needs most.

### **Arachidonic acid**

**AA** is a physiologically significant  $\omega$ -6 fatty acid and is the precursor for prostaglandins and other physiologically active molecules.

### **Linoleic acid**

Other essential fatty acids also come from linoleic acid. Linoleic acid is found in sunflower and safflower oils. Excess linoleic fatty acids can give rise to an excess of certain inflammatory eicosanoids. Linoleic acid is the most important Omega-6 fatty acid since it cannot be directly synthesized by dogs and is used to make other Omega-6 fatty acids.

## **Omega 6 cont.**

### **Dihomo-gamma-linolenic acid**

**DGLA** is the elongation product of  [\$\gamma\$ -linolenic acid](#) (GLA). The [eicosanoid](#) metabolites of **DGLA** are:

series 1 [thromboxanes](#) (thromboxanes with 1 double-bond), via the [COX-1 and COX-2](#) pathways, [prostanoids](#), via the COX-1 and COX-2 pathways, and a 15-hydroxyl derivative that blocks the transformation of [arachidonic acid](#) to [leukotrienes](#).

All of these effects are anti-inflammatory. This is in marked contrast with the analogous metabolites of [arachidonic acid](#) (AA) which are the series-2 thromboxanes and prostanoids and the series-4 leukotrienes. In addition to yielding anti-inflammatory eicosanoids, **DGLA** [competes](#) with AA for COX and lipoxygenase, inhibiting the production of AA's eicosanoids.

Taken orally in a small study, DGLA produced antithrombotic effects. Supplementing dietary GLA increases serum DGLA without increasing serum AA.

### **Delta-6-desaturase**

Without this enzyme D6D, omega-6 fatty acids won't transform themselves into **GLA**. Dogs do possess the D6D enzyme but its activity is often depressed. The loss of this enzyme may also be caused by diabetes, hypothyroidism, **Delta-6-desaturase, cont.**

viral infection or cancer. The enzyme is made with the help of vitamin C, vitamin B, zinc and magnesium; a low amount of these nutrients will decrease the amount of D6D made by the body.

### **Eicosanoids**

The  $\omega$ -6 eicosanoids are generally pro-inflammatory;  $\omega$ -3's are much less so. The amounts of these fats in a person's diet will affect the body's eicosanoid-controlled functions, with effects on [cardiovascular disease](#), [triglycerides](#), [blood pressure](#), and [arthritis](#). Anti-inflammatory drugs such as [aspirin](#) and [NSAIDs](#) act by downregulating eicosanoid synthesis.

## **SAFETY PRECAUTIONS AND INTERACTIONS**

Some medical research suggests that excessive levels of  $\omega$ -6 fatty acids, relative to  $\omega$ -3 fatty acids, may increase the probability of a number of diseases and depression. Excess omega-6 fats interfere with the health benefits of omega-3 fats; in part because they compete for the same rate-limiting enzymes. A high proportion of omega-6 to omega-3 fat in the diet shifts the physiological state in the tissues toward the pathogenesis of many diseases: prothrombotic, proinflammatory and proconstrictive.

Chronic excessive production of omega-6 eicosanoids is associated with heart attacks, thrombotic stroke, arrhythmia, arthritis, osteoporosis, inflammation, mood disorders and cancer. Many of the medications used to treat and manage these conditions work by blocking the effects of the potent omega-6 fat, [arachidonic acid](#). Cats require arachidonic acid because they **cannot** synthesize it from linoleic acid.

## **Non-Essential Fatty Acids Overview**

### **Omega 9**

Unlike [n-3](#) and [n-6](#) fatty acids, [n-9](#) fatty acids are not classed as [essential fatty acids](#) because they can be created by the body from [unsaturated fat](#), and because the lack of an [n-6](#) double bond keeps them from participating in the reactions that form the [eicosanoids](#). Some [n-9s](#) are common components of [animal fat](#) and [vegetable oil](#).

Omega-9 is classified by their chemical structure. Specifically, fatty acids in this group have a "gap" nine carbons from the end of the fatty acid chain. This family includes two major fatty acids called stearic acid and oleic acid.

#### **Stearic acid**

Stearic acid is one of the most abundant fatty acids found in animal fats. Although this fatty acid is a saturated fat, it is a "short chain" fatty acid (only 18 carbons long). Therefore, stearic acid is more likely to be used as energy than to be stored as fat. Also, it is readily converted to another omega-9 fatty acid, oleic acid, which is monounsaturated.

#### **Oleic acid**

Oleic acid is also the most abundant fatty acid found in nature, and is the primary oil produced by skin glands. Although supplementation is not necessary, food sources include olive and almond oils, avocados, and peanut, pecan, cashew, and macadamia oils. [Oleic acid](#) is also a main component of [olive oil](#) and other [monounsaturated fats](#).

Under severe conditions of EFA deprivation, mammals will elongate and desaturate oleic acid to make [mead acid](#). This also occurs to a lesser extent in [vegetarians](#) and semi-vegetarians.

#### **Mead acid**

In a situation of fatty acid deficiency, the body tries to compensate by producing a fatty acid called Mead acid out of the monounsaturated oleic acid. It is a 20-carbon fatty acid with three double bonds named after James Mead, a lipids researcher at the University of California at Los Angeles who first identified it. An elevated level of Mead acid in the body is a marker of EFA deficiency. Mead acid acts as a "filler" fatty acid that cannot serve the functions that the original EFAs are needed for. Mead acid has a full spectrum of protective anti-inflammatory effects; however, the body cannot convert Mead acid into the elongated fatty acids that the body needs for making the various anti-inflammatory prostaglandins.

#### **Eicosenoic acids**

Eicosenoic acids is a long-chain polyunsaturated [fatty acid](#); with 20 carbon atoms that is found in vegetable oils.

#### **Nervonic acid**

Nervonic acid is a monounsaturated [omega-9 fatty acid](#). It has been identified as important in the biosynthesis of nerve cell myelin. It is found in the sphingolipids of white matter in human brain.

Nervonic acid is used in the treatment of disorders involving demyelination, such as [adrenoleukodystrophy](#) and [multiple sclerosis](#) where there is a decreased level of nervonic acid in sphingolipids.

## **Oral Hydration & Electrolytes**

The primary role of electrolytes is to maintain body water and ionic balance. Thus, requirements for elements such as sodium, potassium, and chlorine cannot be considered individually, as it is the overall balance that is important. Electrolyte balance is affected by three factors, namely the balance and proportion of these electrolytes in the diet, endogenous acid production, and the rate of renal clearance. But for true hydration the canine needs glutamine and glutathione which are the two amino acids which are considered the cells “Gate Keepers” allowing nutrients in and toxins out.

### **Balance**

Often termed dietary electrolyte balance or acid-base balance, the effects of deficiency of any one element are often the consequence of alteration to this important balance as it affects osmoregulation.

Most commonly, electrolyte balance is described by the simple formula of  $\text{Na}^+ + \text{K}^+ - \text{Cl}^-$  expressed as mEq/kg (or mEq/g) of diet. Generally, an overall diet balance of 250 mEq/kg is optimal for normal physiologic function.

In most situations, the body attempts to maintain the balance between cations and anions in the body such that physiologic pH is maintained. If conditions in the body result in a shift toward acid or base conditions i.e. surgery, injury, illness, physiologic defense mechanisms alter metabolism to maintain normal pH. Actual electrolyte imbalances rarely occur in healthy animals because these regulatory mechanisms must ensure optimal cellular pH and osmolarity. Electrolyte balance can therefore more correctly be described as the mechanisms that must occur in the body to achieve normal physiologic pH.

### **Ingredients**

#### **Potassium**

Potassium is an essential dietary [mineral](#) and [electrolyte](#), a substance that dissociates into [ions](#) in a solution, making it capable of conducting electricity. Normal body function depends on tight regulation of potassium concentrations both inside and outside of cells. Potassium is important in [neuron](#) function, and in influencing [osmotic balance](#), keeping the body's fluids from becoming too dilute or too concentrated between cells, and the [interstitial fluid](#). It is also the major [cation](#) in animal cells. Potassium is also important in allowing [muscle contraction](#) and the sending of all nerve impulses in animals through [action potentials](#). In [animal cells](#), potassium ions are vital to keeping cells alive.

#### **Deficiency**

A medical condition in which our body fails to retain minimum necessary amount of Potassium required for its day to day functioning is called as Potassium deficiency or hypokalemia. Potassium deficiency (hypokalemia) can be fatal at times if not taken care of. A person may also develop Potassium deficiency due to extra excretion of Potassium or lower quantity of Potassium in daily diet.

#### **Sodium**

Sodium is a [chemical element](#). Sodium ions are necessary for regulation of blood and body fluids, transmission of nerve impulses, heart activity, and certain metabolic functions. Sodium is needed by animals to maintain high concentrations in their blood and extracellular fluids, and is the primary [cation](#) in extracellular fluids in animals and humans. These fluids, such as blood plasma and extracellular fluids in other tissues, bathe cells and carry out

transport functions for nutrients and wastes. It is also a component of many minerals, and it is an [essential element](#) for animal life. As such, it is classified as a “dietary inorganic macro-mineral.”

#### **Deficiency**

A deficiency of sodium leads to a lowering of osmotic pressure and a change in acid-base balance in the body. Cardiac output and blood pressure fall, hematocrit increases, elasticity of subcutaneous tissues decreases, and

adrenal function is impaired. This leads to an increase in blood uric acid levels, which can result in shock and death. A number of diseases can result in sodium depletion from the body e.g., GI losses from diarrhea or urinary losses from renal or adrenal damage.

#### **L-Glutamine**

L-Glutamine is the precursor of glutamic acid, which serves the brain by neutralizing excess ammonia (a byproduct of brain metabolism), thus creating a clearer space for brain activity. L-glutamine has been shown to improve IQ, alleviate fatigue, depression and impotence, as well as speed healing. It also is well-known to decrease the craving for alcohol and is a valuable adjunct in the treatment of alcoholism. These effects may be due to the HGH-releasing (human growth hormone-releasing) properties of the L- form of glutamine, which is, of course, popular with body-builders.

#### **L- Glutathione**

L- Glutathione is the king of all antioxidants. It rules our body's cells, for without it, they would be helpless during the fatal onslaught of free radicals. Glutathione plays a prominent role in regulation of cellular events including gene expression, DNA and protein synthesis, cell proliferation and apoptosis (programmed cell death), and immune response. The presence of glutathione is required to maintain the normal function of the immune system.

#### **Chloride**

The word chloride can also refer to a [chemical compound](#) in which one or more chlorine [atoms](#) are [covalently bonded](#) in the [molecule](#). This means that chlorides can be either [inorganic](#) or [organic compounds](#). Chloride is a chemical the body needs for metabolism, turning food consumed into energy. It also helps keep the body's acid-base balance. The amount of chloride in the blood is carefully controlled by the kidneys.

#### **Deficiency**

A deficiency of chloride causes ataxia. The main sign of hypokalemia is an overall muscle weakness characterized by weak extremities, poor intestinal tone with intestinal distention, cardiac weakness, and weakness and ultimately failure of the respiratory muscles. Hypokalemia is apt to occur during severe stress. Plasma protein becomes elevated, causing the kidney, under the influence of adrenocortical hormone, to discharge potassium into the urine. During adaptation to the stress, blood flow to the muscle gradually improves, and the muscle begins to retrieve lost potassium. As liver glycogen is restored, potassium returns to the liver. This may result in temporary prolongation of the hypokalemia.

#### **Citrate**

A citrate can refer either to the [conjugate base](#) of [citric acid](#), or to the [esters](#) of citric acid. Citric acid acts as a mild chelating agent.

#### **Zinc**

Zinc stimulates the activity of approximately 100 enzymes, which are substances that promote biochemical reactions in the body. Zinc supports a healthy immune system, is needed for wound healing, helps maintain the sense of taste and smell, and is needed for DNA. Zinc is found in higher concentrations in meat and bone than it is in plant sources.

Zinc is an essential element, necessary for sustaining all life, found in almost every cell. It is estimated that 3,000 of the hundreds of thousands of proteins in the body contain zinc [prosthetic groups](#), one type of which is the so-called

[zinc finger](#). In addition, there are over a dozen types of cells in the body that secrete zinc [ions](#), and the roles of these secreted zinc signals are now being actively studied. Zinc ions are now considered to be [neurotransmitters](#). Cells in the [salivary gland](#), [prostate](#), [immune system](#) and [intestine](#) use zinc signaling. Zinc is an activator of certain

enzymes, such as [carbonic anhydrase](#). Carbonic anhydrase is important in the transport of carbon dioxide in vertebrate blood.

Zinc is also involved in [olfaction](#): the [olfactory receptors](#) contain zinc binding sites and a deficiency in zinc causes [anosmia](#).

#### **Deficiency**

Zinc is not considered to be highly absorbable. Studies show that between 5% and 40% of ingested zinc is actually absorbed. Calcium also binds zinc, and zinc deficiencies can be produced when excess amounts of calcium are fed. Dogs or cats with inflammatory bowel disease may develop zinc deficiency because of lack of absorption. Diseases or conditions that involve intestinal malabsorption promote zinc losses. Fecal losses of zinc caused by diarrhea are one contributing factor. Zinc salts are effective against [pathogens](#) in direct application. [Gastroenteritis](#) is strongly attenuated by ingestion of zinc, and this effect could be due to direct antimicrobial action of the zinc ions in the GI tract, or to absorption of the zinc and re-release from immune cells (all [granulocytes](#) secrete zinc), or both.

#### **SAFETY PRECAUTIONS AND INTERACTIONS**

Toxicities to zinc due to over supplementation are very rare. Zinc toxicities can occur, however, if an animal would swallow pennies minted since 1982, zinc hardware on transport cages, zinc ointment, or eat or drink from galvanized containers.

#### **Alanine**

Alanine is a non essential [amino acid](#), and found in a wide variety of foods, but is particularly concentrated in meats. It occurs in high levels in its free state in plasma, and is produced from pyruvate by transamination. Alanine is involved in sugar and acid metabolism, increases immunity, and provides energy for muscle tissue, brain, and the central nervous system. Alanine (abbreviated as Ala or A) is an  $\alpha$ -[amino acid](#) with the [chemical formula](#)  $\text{HO}_2\text{CCH}(\text{NH}_2)\text{CH}_3$ . The L-isomer is one of the 20 [proteinogenic amino acids](#), i.e. the building blocks of [proteins](#). D-alanine occurs in bacterial cell walls and in some peptide antibiotics. The  $\alpha$ -[carbon](#) atom of alanine is bound with a [methyl](#) group ( $-\text{CH}_3$ ), making it one of the simplest  $\alpha$ -amino acids with respect to molecular structure and also resulting in alanine being classified as an [aliphatic](#) amino acid. The methyl group of alanine is non-reactive and is thus almost never directly involved in protein function.

Alanine plays a key role in [glucose-alanine cycle](#) between tissues and liver. In muscle and other tissues that degrade amino acids for fuel, amino groups are collected in the form of glutamate by [transamination](#). Glutamate can then transfer its amino group through the action of [alanine aminotransferase](#) to [pyruvate](#), a product of muscle [glycolysis](#), forming alanine and [alpha-ketoglutarate](#). The alanine formed is passed into the blood and transported to the liver. A reverse of the alanine aminotransferase reaction takes place in liver. Pyruvate regenerated forms glucose through [gluconeogenesis](#), which returns to muscle through the circulation system. Glutamate in the liver enters [mitochondria](#) and degrades into [ammonium ion](#) through the action of [glutamate dehydrogenase](#), which in turn participate in the [urea cycle](#) to form [urea](#).

#### **Niacin**

**Niacin:** Niacin plays a role mainly in helping enzymes function properly. Niacin is found in adequate levels in meats and meat by-products and is very low in vegetables and grains.

Niacin derivatives are involved with detoxification of xenochemicals, DNA repair, and the production of steroid hormones in the adrenal gland. Niacin, also known as nicotinic acid, Vitamin B3, or 3-pyridine carboxylic, is involved in the oxidative release of energy from food, protects the skin and helps improve circulation. Niacin is an essential component of mammalian diet. It is the pellagra-preventing factor of vitamin B. The amide, nicotinamide is incorporated into nicotinamide adenine dinucleotide.

## **SAFETY PRECAUTIONS AND INTERACTIONS**

Estimates of maximum tolerable levels of niacin compounds are not possible because of the limited definitive quantitative data presently available. The level of 350 mg nicotinamide/kg of BW/day is presumed safe for chronic exposure. Nicotinic acid may be tolerated at intakes as great as four times this level.

normal (macrocytic). The quantity of [white blood cells](#) may also be reduced. Vitamin B12 is usually included in the diet and is found in organ meats.

### **Deficiency in Gastrointestinal Disease**

Cobalamin (Vitamin B12) is a water-soluble, cobalt-containing vitamin with an important role in biochemical processes referred to as single carbon transfers. During these reactions, functional units such as methyl groups (-CH<sub>3</sub>) are transferred onto or between biologically important compounds. Cobalamin is a co-factor for at least three enzymes that carry out these types of reactions, acting as a transitional carrier of the single carbon group.

In companion animal medicine, most attention to cobalamin has been directed towards its use as a diagnostic marker for gastrointestinal disease. Recent evidence from studies at the Gastrointestinal Laboratory have also shown that supplementation of cobalamin is important to get the best response to therapy for gastrointestinal disease.

In animals with reduced cobalamin absorption, regardless of the cause, it is reasonable to expect that eventual depletion of bodily cobalamin stores will occur and cobalamin deficiency will ensue. As all cells in the body require cobalamin for single carbon metabolism, it has been hypothesized that cobalamin deficiency may actually contribute to the clinical signs and manifestations of gastrointestinal disease in some patients. Studies of radiolabelled cobalamin in cats have demonstrated that the half-life of this compound is significantly reduced with gastrointestinal disease.

A recent study has examined the effect of cobalamin supplementation on the outcomes of treatment for feline patients with severe cobalamin deficiency and histories suggesting chronic gastrointestinal disease.<sup>5</sup> In this study, serum concentrations of methylmalonic acid normalized following parenteral cobalamin supplementation, indicating that cobalamin deficiency was the cause of the high methylmalonic acid in serum. There was an overall weight gain in these patients, and a decrease in the frequency of clinical signs such as vomiting and diarrhea. During the course of the study, there was no change to the therapeutic regime other than the introduction of parenteral cobalamin supplementation.

Dogs with exocrine pancreatic insufficiency will commonly present with subnormal serum cobalamin concentrations.

Therapy with bovine pancreatic enzyme extracts is not sufficient to restore cobalamin absorption in dogs with EPI, as intrinsic factor appears to be species specific. Failure to absorb cobalamin in dogs with EPI may be due to all three potential causes of low serum cobalamin. Pancreatic secretion of intrinsic factor is reduced or absent, secondary bacterial overgrowth of the intestine is common, and the mucosa may be compromised by the presence of excessive bacterial numbers and toxic metabolites. Dogs with exocrine pancreatic insufficiency should be considered at high risk for the development of cobalamin deficiency. As clinical signs of cobalamin deficiency include chronic wasting or failure to thrive, malaise, and gastrointestinal signs such as diarrhea, serum cobalamin concentration should be measured in any dog with poor response to enzyme replacement therapy for EPI.

## **SAFETY PRECAUTIONS AND INTERACTIONS**

Toxicities are of no concern.

### **Organic Agave Syrup**

**Agave syrup** (also called **agave nectar**) is a natural sweetener made from *agave americana* plant (also called Century Plant), and marketed as a healthful natural sugar substitute and excellent natural energy. It is produced in Mexico. Agave syrup is similar to honey in color and texture, though less viscous. It is available in light or dark colors, the light being filtered. It has the highest digestibility and energy factors of any natural and organic syrups. It's absorption starts immediately and is nearly 100% digestible. Agave Syrup gives a steady sustained energy release. Although far superior to rice based sweeteners its syrupy nature and higher price typically limits its use to premium eatable products.

#### **Agave Plant Species**

There are several hundreds species of Agave. A few of them include Agave asperrima, Agave americana and Agave striata.

#### **Chemical composition of Agave plant**

Agave has [saponins](#) and fructans. [Inulin](#) is a type of fructan that has many health benefits. Saponins are found in many plant roots, the most famous being ginseng.

**Vitamin C** is required in the synthesis of collagen in connective tissue, neurotransmitters, steroid hormones, carnitine, conversion of cholesterol to bile acids and enhances iron bioavailability. Ascorbic acid is a great antioxidant and helps protect the body against pollutants. Because vitamin C is a biological reducing agent, it is also linked to prevention of degenerative diseases - such as cataracts, certain cancers and cardiovascular diseases.

**Magnesium** is necessary for calcium and vitamin C metabolism. Magnesium helps with formation of bone and teeth and assists the absorption of calcium and potassium. Where calcium stimulates the muscles, magnesium is used to relax the muscles. It is essential for effective nerve and muscle functioning and important for converting blood sugar into energy. It is further needed for cellular metabolism and the production of energy through its help with enzyme activity. It is used for muscle tone of the heart and assists in controlling blood pressure. Together with vitamin B 12, it may prevent calcium oxalate kidney stones.

**Potassium** is an essential electrolyte contributes to heart health, changes glycogen to glucose, and promotes healing. It is needed for growth, building muscles, transmission of nerve impulses, heart activity etc. Potassium, together with sodium - potassium inside the cell and sodium in the fluid surrounding the cell, work together for the nervous system to transmit messages as well as regulating the contraction of muscles. Because most diets are low on Potassium and high on Sodium we provide a higher Potassium level promoting proper body metabolism.

**Sodium** needed for electrolyte replenishment. Sodium is an electrolyte in the body and is required in the manufacture of hydrochloric acid in the stomach, which protects the body from any infections that may be present in food. Since the American diet is extremely high in sodium we take this fact into account and reduce our level to 100mg.

**Glucosamine HCL** essential for lubricating and rebuilding joints by contributing to the formation of cartilage. Cartilage cushions joints. As wear and tear occurs, the body's ability to replace cartilage slows or ceases, resulting in osteoarthritis. After the age of 35 it is recommended that a person take a minimum of 1500mg per day. Glucosamine is found in Wilderness Athlete™ energy bars (1000mg) as well as the HYDRO<sup>2</sup>max (250mg).

**Golden Root Extract (Siberian Rhodiola Rosea root extract)** is to combat fatigue and anemia through more efficient oxygen utilization. Benefits related to mental and physical performance have been clinically demonstrated exclusively using only standardized Siberian Rhodiola Rosea root extract.

**L-Glutamine** It is converted to glutamic acid in the brain, which is essential for cerebral functions, and increases the amount of GABA (gamma-amino butyric acid), which is required for brain functioning and mental activity. It is used in the muscles for the synthesis of muscle proteins, and is of use for the treatment of wasting muscles after illness or post-operative care.

**L-Glutathione** It is a powerful antioxidant and detoxifies the harmful compounds in the liver, where it is then excreted through the bile. The liver also excretes glutathione directly into the bloodstream where it is used to help maintain the integrity of red blood cells, as well as protecting white blood cells. Glutathione is also found in the lungs and intestinal tract where it assists in carbohydrate metabolism as well as breaking down oxidized fats. It is also used to prevent oxidative stress in most cells and helps to trap free radicals

**Coenzyme Q-10** an essential amino acid needed for basic cell function and repair. It has antioxidant qualities assisting the flow of oxygen within cells, assistance with cardiovascular functioning, the production of energy, its assistance with absorption of other nutrients as well as its immune boosting properties.

**Chicken Flavoring**

The chicken flavoring is natural: however it is derived from vegetables, not animals.

## **Natural Calming Aids**

Liquid or tablet forms may offer a calming support to pets during periods of anxiety, nervousness, tension or stress. They are not recommended for use prior to surgery. Safe use in animals intended for breeding has not been proven. Caution should be exercised when using calming aids with MAO inhibitors. These products may also add to the effects of anesthetics.

### **Tablet Ingredient Descriptions**

#### **Chamomile**

Chamomile is an annual herb found in southern Europe and northern Asia. The medicinal portion is the flower. Its medicinal activities include antispasmodic, intestinal gas expulsion, an anti-inflammatory, sedative, anti microbial, stimulate digestion, heal wounds, and expels worms.

Chamomile's high content of the amino acid tryptophan has been used for sleeplessness and insomnia since the 1600's. It can also help restore an exhausted nervous system, and may be soothing to an upset stomach, easing digestion. It is commonly used as a mild sedative to calm the nerves, reduce anxiety, and induce a state of pleasant relaxation without disrupting normal function or interfering with motor coordination. Chamomile's effectiveness can be due to its anti-inflammatory properties, soothing ulcers and reducing gastritis and other mucous membrane inflammations.

In the United States, Chamomile has been classified as GRAS (Generally Recognized As Safe) by the Food and Drug Administration. However, please be aware of the safety precautions.

#### **SAFETY PRECAUTIONS AND INTERACTIONS**

Possible interactions relate to the antiarrhythmic agent quinidine, which may increase the hypoprothrombemic effect of Chamomile. Conversely, the anti-inflammatory activity of Chamomile can be seriously inhibited by phenobarbital as well as by certain other sedatives and hypnotics, such as chloral hydrate and meprobamate. This is also true of beta-adrenergic blocking agents such as propranolol. Vitamin K, menadione, and menadiol sodium diphosphate may antagonize the anticoagulant effect of coumarins. Although the coumarin content of chamomile is not high at normal usage levels, it is important to note that coumarins can affect the action of almost any drug. It should also be noted that the presence of azulenes in chamomile may interfere with the actions of bradykinin, histamine, acetylcholine, and serotonin. We recommend that Chamomile not be used if the above conditions are a concern. Precautions should be used when prescribing for cats.

#### **Passion Flower**

Phytochemists have isolated multiple components from the aerial portions of the Passion Flower plant, including several flavonoids that are believed to exhibit a sedative effect in the Central Nervous system: Vitexin, Isovitexin, Chrystin, and Orientin. Chrysin is a monoflavonoid that is considered to be the primary active compound derived from Passion Flower. In laboratory settings, scientists have demonstrated that Chrysin works as a partial agonist of the central benzodiazepine receptors in the brain. It is thought that the combination of flavonoids in Passion Flower contribute to its effectiveness as an anxiolytic which helps to promote relaxation, soothe tension and relieve occasional anxiety and panic caused by emotional stress. Passion Flower has a long history of use among Native Americans in both North and Central America. It is used to treat insomnia, hysteria, and epilepsy, and is also valued for its painkilling properties. It has been found to contain beta-carboline harmala alkaloids which are MAOis with anti-depressant properties.

In the United States, Passion Flower has been classified as GRAS (Generally Recognized As Safe) by the Food and Drug Administration.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

Excessive doses may cause sedation and may potentiate MAOI therapy. As uterine stimulant activity in animal studies has been reported, it is not recommended for pregnant animals.

### **Thiamine Mononitrate**

Similar to some other B complex vitamins, thiamine is considered an "anti-stress" vitamin because it is believed to enhance the activity of the immune system and improve the body's ability to withstand stressful conditions.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

Oral vitamin B1 is generally nontoxic. Stomach upset can occur at very high doses (much higher than the recommended daily amount). Taking any one of the B complex vitamins for a long period of time can result in an imbalance of other important B vitamins. For this reason, it is generally important to take a B complex vitamin with any single B vitamin, if it is given on a regular basis.

### **Ginger**

Ginger common uses: indigestion, flatulence, and colic. Used to increase peripheral circulation. May help in some cases of motion sickness. In small animals, the pungent constituents have been shown to be cardio tonic, fever reducing, analgesic, antitussive, and sedative.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

It has been reported to tend to increase the tone of the heart muscle and blood vessels (cardio tonic) and to inhibit blood clotting in vitro. It also has hypoglycemic activity in in vitro studies. Excessive doses may interfere with existing cardiac, antidiabetic, or anticoagulant therapies. Doses that greatly exceed those normally found in foods should not be administered during pregnancy or lactation.

### **L-Tryptophan**

It is one of the 20 amino acids in the genetic code. Tryptophan is a component of many plant and animal proteins, and a normal part of the diet that humans and animals must get from outside sources. Foods that are considered sources of tryptophan are dairy products, beef, poultry, barley, brown rice, fish, soybeans, and peanuts. It is an essential amino acid that is required to produce vitamin B3 (niacin), and a precursor for serotonin, melatonin, and niacin.

Tryptophan has been found to increase brain levels of serotonin, a calming neurotransmitter when present in moderate levels, and/or melatonin, a sleep-inducing hormone secreted by the pineal gland in response to darkness or low light levels. Serotonin neural circuits also help counterbalance the tendency of brain dopamine and nonadrenaline circuits to encourage over-arousal, fear, anger, tension, aggression, violence, obsessive-compulsive actions, over-eating (especially carbohydrates), anxiety and sleep disturbances.

Clinical research tended to confirm tryptophan's effectiveness as a natural sleep aid and for a growing variety of other conditions typically associated with low serotonin levels or activity in the brain. Studies with humans and animals conducted over the past 30 years show that serotonin nerve circuits promote feelings of well-being, calm, personal security, relaxation, confidence and concentration.

In the work by Dr. Richard Wurtman at MIT, tryptophan showed considerable promise showing a reduction of impulsive, violent, manic, compulsive behaviors and disorders.

## **Liquid Ingredient Descriptions**

Liquid calming agents usually contain flower essences in an alcohol preservative base. They are not extracts but the essence of the flowers, and come in separate formulas for dog or cats.

Jeffrey R. Cram, Ph.D conducted a study on flower essences. He reported: Certain flower essences are thought to have an antadoting effect on the impact of high levels of environmental stimulation. Using a randomized double blind experimental design, this study explored the effects of two flower essence formulas (Yarrow Special Formula and Five Flower Formula) on the intense environmental stimulation of fluorescent lights and its concomitant electromagnetic fields (EMF). Twenty four subjects (N=8 per cell) were monitored using a 19 channel qEEG system, along with the activity of six sEMG sites (Frontal, C2 (mastoid to mastoid), Cervical (C4 paraspinals), Thoracic (T6 Paraspinals), Lumbar (T12 paraspinals) and Sacral (L1 Paraspinals)). A 12 minute study was conducted which assessed baseline activity; reaction to the flower essence or placebo; reaction to the high

intensity light stimulation; and concluded with a recovery period. The artifacted qEEG and sEMG data were submitted to standard statistical analysis (ANOVA). The results of the study show EEG activation of the frontal lobes area to the photic stimulation, but only for those individuals who received the Placebo preparation. Concurrent activation of the T6 paraspinals was also noted for only the Placebo control group as well. This demonstrates that the stress response was seen only in the Placebo group. Here the executive and premotor functions of the frontal lobes activate to determine the course of action to the perceived threat, while the subject concurrently extended their chest in preparation for fight or flight. The two flower essence groups showed no similar stress response. Thus flower essences are demonstrated to antidote environmental stressors.

#### **Ilex Aqu**

Ilex aqu is English Holly. It reverses thoughts of envy, jealousy, hatred, intense anger, revenge and suspicion.

#### **Impatiens Glan**

Impatiens is given to nervous, impatient, unforgiving, cruel, anxious or agitated animals. It can be used for animals that are overly anxious at feeding time, before races, or animals exhibiting nervous trembling. It may be used on epileptic animals and to alleviate emotional or physical discomfort.

#### **Helianthemum Num**

Rock Rose is for any form of terror and panic. Rock Rose is especially good during a storm for potential runaways. It is also helpful after accidents, injuries or terrifying events because it gives animals courage. It works on animals who are easily excited.

#### **Omithogalum Umb**

Star of Bethlehem serves animals that are experiencing current or past traumas, both physical and emotional. It is effective in animals needing comfort.

### **SAFETY PRECAUTIONS AND INTERACTIONS**

No known side effects.

# Summary

## Aches , Pains, Fevers

- White Willow Bark natural, aspirin free, helps eliminate pain
- Treats mild fevers, colds, infections
- Natural ingredients for older dogs, will not affect the kidneys or liver.
- Yucca is a quality anti-inflammatory that is necessary in the joint rebuilding process
- MSM helps with inflammation

## Digestive Enzymes & Probiotics Ingredients

- Digestive enzymes assist in the breakdown of food, enabling nutrients to be absorbed into the bloodstream. Nutrients are essential for all cellular functions. They turn food into energy and unlock this energy for use in the pet's body, while improving blood and immune system function.
- Adding digestive enzymes may contribute in boosting depleted organ enzyme banks.
- Probiotics provide "good bacteria" to help the animal's body digest food and maintain a healthy metabolism.

## Ear Wash Ingredients

- Tea Tree Oil is antimicrobial, possibly antiviral, and weakly antimycotic. Good for disinfecting skin and fungal infections. Safe for cats at this level in the product.
- Witch Hazel is a natural astringent, anti-inflammatory and hemostatic.
- Boric acid is used as an astringent and antiseptic. It is also antibacterial and antifungal.
- Glycerine helps loosen ear wax.
- Echinacea extract is immunostimulating, anti-inflammatory, cytokine stimulating and a collagen protectant.

## Fatty Acids

- Fatty acids play a part in many metabolic processes.
- A deficiency or a wrong balance/ ratio in type, may be a factor in many illnesses.
- Omega 3's are derived from fish and fish oil, walnuts, flax and hempseed. Plant-derived PUFA's (polyunsaturated fatty acids) require de-saturation to form EPA and DHA. EPA - required for the production of a special group of substances in the body called prostaglandins, which control blood clotting and other arterial functions. DHA - a major component of the human brain tissues and the retinal tissues of the eyes. It also serves the other important function of the transmission of nerve impulses in the nervous system. Fish oils already contain EPA and DHA and require no conversion. Omega 3's minimizes inflammation.
- Omega 6's are derived from nuts, cereal, whole-grain bread, most vegetables oils, soy, eggs, and poultry. Chronic excessive production of Omega 6 eicosanoids is associated with heart attacks, thrombotic stroke, arrhythmia, arthritis, osteoporosis, inflammation, mood disorders and cancer. Omega 6, following de-saturation, produces AA through delta-6-desaturase enzyme in the liver. Cats livers lack this enzyme and benefit more from DHA enriched Salmon Oil added directly in the diet.

- Omega 9's are not classed as essential fatty acids because they can be created by the body from unsaturated fat, and because the lack of an  $n-6$  double bond keeps them from participating in the reactions that form the eicosanoids. Some  $n-9$ s are common components of animal fat and vegetable oil.

## **Joint Support Ingredients**

- Chondroitin does the best job of supplying the necessary glycosaminoglycans (GAGs) of any nutrient available.
- Glucosamine is superior at its ability to build collagen and proteoglycans. Its mechanism of action is quite simple: providing the regulatory stimulus and raw material for synthesis of GAGs.
- Yucca is a quality anti-inflammatories that are necessary in the joint rebuilding process.
- The antioxidants vitamin E (fat soluble) and Ester-C<sup>®</sup> (water soluble) work together to eliminate obstacles that would obstruct the cartilage and synovial regeneration process.
- Enzymes aid in the digestion of the joint support ingredients.
- Super Oxide Dismutase (SOD) enhances the body's antioxidising enzymatic action, helps reduce degenerative related diseases, and reduces free-radical waste and build up. Has some anti-inflammatory properties.

## **Natural Calming Aid Ingredients**

- Chamomile, Passion Flower, Thiamine Mononitrate, Ginger and L-Tryptophan are effective calming ingredients.
- Certain flower essences are thought to have an antadoting effect on the impact of high levels of environmental stimulation. Common ones include: Ilex aquifolium (English Holly), Impatiens glandulifera (Impatiens), Helianthemum nummularium (Rock Rose), and Omithogalum umbrosum (Star of Bethlehem) preserved in a 13% alcohol preservative base.

## **Oral Electrolyte Ingredients**

- Helps maintain body water and ionic balance.
- Potassium ions are vital in keeping cells alive.
- Sodium ions are necessary for regulation of blood and body fluids.
- Chloride is a chemical needed for metabolism and to balance the body's acid base.
- Citrate acid acts as a mild chelating agent.
- Zinc stimulates the activity of approximately 100 enzymes and supports a healthy immune system.
- Alanine plays a major role in the transfer of nitrogen from peripheral tissue to the liver, aids in the metabolism of glucose, and strengthens the immune system by producing antibodies.
- Niacin is a B vitamin, playing a role in helping enzymes function properly. It found in adequate levels of meats and meat by-products.
- Vitamin B 12 improves the animal's appetite. It is necessary for bone marrow to produce red blood cells. It is found naturally in organ meat.
- Phosphoric acid is used in hydroponics pH solutions to lower the pH of nutrient solutions.
- **L-Glutamine** It is converted to glutamic acid in the brain, which is essential for cerebral functions, and increases the amount of GABA (gamma-amino butyric acid), which is required for brain functioning and mental activity. It is used in the muscles for the synthesis of muscle proteins, and is of use for the treatment of wasting muscles after illness or post-operative care.

- **L-Glutathione** It is a powerful antioxidant and detoxifies the harmful compounds in the liver, where it is then excreted through the bile. The liver also excretes glutathione directly into the bloodstream where it is used to help maintain the integrity of red blood cells, as well as protecting white blood cells. Glutathione is also found in the lungs and intestinal tract where it assists in carbohydrate metabolism as well as breaking down oxidized fats. It is also used to prevent oxidative stress in most cells and helps to trap free radicals .
- **Coenzyme Q-10** an essential amino acid needed for basic cell function and repair. It has antioxidant qualities assisting the flow of oxygen within cells, assistance with cardiovascular functioning, the production of energy, its assistance with absorption of other nutrients as well as its immune boosting properties.

### **Urinary Tract Incontinence Support**

- Urethral Sphincter Mechanism Incompetence is the most commonly diagnosed cause of urinary incontinence.
- The urethral sphincter smooth muscles contain receptors that can be affected by hormones.
- PPA and DES are common drugs given to dogs for this condition, but unfavorable adverse conditions in humans have been documented.
- Phytoestrogens, dietary estrogens found in plants, offer an alternative to DES and PPA.
- When using phytoestrogens you should allow 4-6 weeks for nutrient levels to balance in cellular structures
- **Rehamnnia** brings blood to the kidneys and replenishes the vital essence.
- **Wild Yam Root** has a diuretic effect, antispasmodic action, and contains natural estrogen.
- **Pumpkin Seed** can improve bladder and urethra function.
- **Dang Gui Shen** is an effective blood tonic and is a phyto-estrogenic precursor.
- **Licorice** contains phytoestrogens and harmonizes the other herbal ingredients in a formula.
- **Oregon Grape Root** is a natural antibiotic remedy for infections of the bladder, kidneys, and urethra.
- **Marshmallow Root** provides a soothing, lubricating protective barrier between mucous membranes and substances which contribute to irritation.
- **Cranberry Max** helps minimize bacterial colonization of the bladder mucosa by making the bladder lining inhospitable to bacteria.
- **Ester-C** helps make the urine more acidic so it is inhospitable to bacteria, and is an immune builder.
- **Alfalfa** is used to treat disorders related to the digestive tract and kidneys, and as a diuretic for increased urination.

### **Urinary Tract Infections Support Ingredients**

- Helps to naturally alleviate urinary tract infections.
- Helps prevent bacterial colonization on the bladder lining.
- **Marshmallow Root** provides a soothing, lubricating protective barrier between mucous membranes and substances which contribute to irritation.
- **Oregon Grape Root** natural antibiotic remedy for infections of the bladder, kidneys, and urethra.
- **Urinary Comfort** helps minimize bacterial colonization of the bladder mucosa by making the bladder lining inhospitable to bacteria.
- **Echinacea** is a natural immune system booster.
- **Ester-C<sup>®</sup>** makes the urine more acidic and therefore more inhospitable to bacteria.

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