The Benefits of Whole Food Nutrition in Veterinary Medicine

Clinical Use of Whole Food Nutrients in Veterinary Practice

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Nutrition is the foundation of optimal health. Innumerable studies and observations over the centuries have pointed out the importance of nutrition in maintaining health. These studies have correlated deficiencies of vitamin C with scurvy (Firth and Marvan, 2001; Rajakumar, 2001), thiamin with beriberi (Tallaksen and Bovim, 1998; Carpenter and Sutherland, 1995), niacin with pellagra (Ishikawa, 2000; Malfait et al., 1993), B vitamins with Alzheimer's and heart disease (Selhub et al., 2000; Pautas et al., 1999; Zeitlin et al., 1997), fat-soluble vitamins with liver disease, cholestasis, and inflammatory bowel disease (Shirahata, 1999; Bousvaros et al., 1998), minerals with growth inhibition (Clausen and Dorup, 1998;), and antioxidants with nutritional amblyopia and chronic diseases (Weisburger, 2000; Lessell, 1998).

It is only in the modern era that our foods are available primarily in a processed form. Our foods are now cooked, pasteurized, refined, exposed to pressure, and mixed with preservatives to prolong shelf life and additives to alter color, texture, and taste. It is clearly recognized that processing food in this way damages or destroys vital nutrients (Ghebremeskel and Crawford, 1994; Schroeder, 1971). Extensive documentation of the world-wide effects of processed foods on human health was compiled by Dr. Weston Price (1945, 1997). Price observed cultures throughout the world and found that health problems developed in epidemic proportions when native cultures changed from traditional foods to modern, processed diets.

Likewise, in a decade long, multi-generational study in cats comparing the effects of cooked, raw, and raw and cooked food combinations, Dr. Francis Pottenger (Pottenger and Pottenger, 1995) found that multiple degenerative disorders developed in cats eating mostly cooked foods. These disorders became progressively worse in the cooked food group of cats as this feeding approach was continued over succeeding generations. The list of disorders is long and includes skeletal abnormalities of the skull and long bones, cardiac problems, poor eyesight, thyroid disorders, arthritis, respiratory disease, allergies, dental disease, and infections of internal organs like the liver and kidneys. Much of the pattern of disease noted by Pottenger is mirrored in the diseases seen in veterinary practice today.

These studies and others (Biourge, 1997; Pedersen, 1992; Freeman, 1998; Ogilvie, 1998) highlight the critical importance of nutrition for optimal health and provide solid evidence that essential nutritional factors are lost or altered during routine food processing.

Processed Foods

Manufacturers of foods for human consumption attempt to compensate for the loss of nutrients in processed foods by adding synthetic or isolated factors back to the food (Hermus and Severs, 1999; Leklem et al., 1980). Unfortunately, other chemical additives, are included to alter the color, texture, and flavor of foods, some of which have questionable effects on health (Reus et al., 2000; Swanson and Kinsbourne, 1980). The same situation exists in the pet food industry; pet foods are exposed to heat and pressure during manufacturing and contain numerous additives. Compared to the varied food choices available to humans, pets consume a diet that generally consists only of the processed foods offered by pet food manufacturers. In an attempt to produce a single food that fully meets the nutritional needs of the intended species, pet food manufacturers add synthetic or isolated nutrients to their products.

Clearly, most of the current pet food options run counter to the ancestral norm of consuming whole foods in their raw, unadulterated state, as all animals did prior to domestication by humans. It is important to recognize that feeding processed foods is a historically recent phenomenon and so the full biological impact has yet to be realized. Many factors have contributed to our current feeding method, not the least of which is pet owner convenience. Food manufacturer advertising has a powerful influence, as does the pet owner's desire to provide the balanced diet that is recommended by veterinarians and nutritionists (Dzanis, 1998; Brown, 1994; Reotutar, 1989; Kallfelz, 1989).

As our recognition of nutritional factors and our understanding of pathological processes continues, novel pet foods are constantly being developed to act as sole or adjunctive therapies for a variety of disease conditions in pets (Scanlan, 2001; Watson, 1998; Kallfelz, 1989; Jacob et al., 2002). While there is evidence to support the use of these foods clinically, there is a commonly overlooked and disturbing aspect of feeding processed food as the sole source of nutrition. Even though these foods are considered nutritionally complete, actual individual long-term consumption has shown the fallacy of this (Morris and Rogers, 1994). Identification of taurine deficiency as a causative factor in the development of feline cardiomyopathy (Pion et al., 1987) and feline central retinal degeneration (Barnett and Burger, 1980; Hayes et al., 1975) in cats fed premium cat foods, previously considered to offer complete nutrition, underscores this point.

The recognition that feeding pets processed foods may contribute to the development and progression of diseases has led to a feeding paradigm in the holistic veterinary community that involves the use of raw foods in the diet, a fact that is not without controversy for a variety of reasons. However, many veterinarians are reporting obvious clinical benefits from the consumption of primarily unprocessed diets confirming the results of the Pottenger study.

Composition of Whole Food

Whole food is a complex, integrated group of closely associated substances. These substances include vitamins, minerals, phytochemicals, enzymes, fats, carbohydrates, and nucleotides, as well as currently unknown micronutrients. Each food is a unique combination of these factors at different concentrations. For example, black currant contains high levels of vitamin C and bioflavonoids (Duke, 2001; Mikkonen et al., 2001; Young et al., 1999; Romero Rodriguez et al., 1992), wheat germ and bran contain vitamin E and vitamin B6 (Duke, 2001; Barnes, 1982; Barnes and Taylor, 1980; Lindberg et al., 1983), bovine kidney contains vitamin A (Kato et al., 1984; Plopper et al., 1977; Smith et al., 1975), alfalfa contains numerous trace minerals (Duke, 2001; Townsend et al., 1999; Sadiq and Abdurrehman, 1999), and rice bran contains inositol and the vitamin B complex (Jariwalla, 2001; Rao, 2000).

Crop growing conditions can modify concentrations of food constituents (Wang and Zheng, 2001; Yang and Lee, 2001; Leonardi et al., 2000; McKeehen et al., 1996; Frick et al., 1994; Ivanova et al., 1993). It is known that hydroponic growing conditions, in which mixtures of nutrients are "force fed" to plants, cause the reduction of several nutrients in tomatoes (Premuzic et al., 1998). Additionally, greenhouse grown vegetables have been shown to be lower in chlorophyll, vitamin C, crude fiber, and minerals than field grown vegetables (Yao et al., 1999). Recent research has also shown an increase in nutrient density in organically produced foods (Worthington, 2001; Sundrum et al., 2000; Worthington, 1998).

Other factors that influence nutrient composition of plants include the variety (Kurilich et al., 1999; Kushad et al., 1999) and whether the plant is open-pollinated or a hybrid (King, 2002). Composition of foods derived from animal sources are affected in a similar fashion. For example, it has been shown that cattle fed on pasture, dry feeds, or in a feedlot have differences in the biochemical profile of the adrenal gland (Loerch and Fluharty, 1999; Gwazdauskas et al., 1986; Phillips et al., 1982), indicating variation in the nutritive benefits of using that tissue as a food source.

Select foods can be utilized to support specific physiological processes through recognition of the food constituents (Ogilvie, 1998; Biourge, 1997). This must be combined with an understanding of the biochemistry of the cellular process of interest. For example, coldwater fish oil containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be used to modulate inflammation through inhibition of the 5-LOX (lipoxygenase) pathway that converts arachidonic acid to inflammatory leukotrienes in neutrophils and monocytes (Calder, 2001; Keicher et al., 1995).

Manufactured Pet Foods

For economic reasons, mass-produced pet foods must rely on food ingredients of variable quality (Morris and Rogers, 1994). Further, many popular pet foods are produced using formulas in which ingredient choices are based on cost and availability rather than quality. This means that while the label analysis remains constant, the protein and other sources may fluctuate significantly. Obviously, this situation compounds concern about the nutrient quality of each food's source ingredients. Further, use of these pet foods for their therapeutic value may provide variable and unreliable results. In response to this, premium pet food manufacturers have developed products with fixed formulas validated through the Association of American Feed Control Officials (AAFCO) feeding studies. Generally, these products contain high-quality ingredients that are consistent from one production batch to the next (Huber et al., 1991) and tend to be more costly for the consumer.

The importance of this approach is highlighted in studies comparing a popular national brand of dog food with lower priced foods; these studies gave results indicative of nutritional deficiency in the lower priced foods (Huber et al., 1986). When growing puppies were fed the lower priced foods, they consumed greater amounts of food per pound of weight gain than did those fed the national brand. More significantly, the puppies fed the lower grade foods had graying hair coats and a lower hematocrit, hemoglobin, and serum albumin. With the lower priced foods, protein digestibility was low, suggesting that poor-quality protein sources were used and/or that heat damage occurred during processing. Zinc-responsive dermatosis has also been reported in dogs fed generic food brands (Sousa et al., 1988). These studies demonstrate some obvious health impacts of pet foods made with poor-quality ingredients.

Pet foods are designed to contain a variety of nutrient sources, including:

- **Animal protein:** Commonly derived from beef, chicken, lamb, and their by-products
- **Non-animal protein:** Corn gluten meal, soy flour, and wheat germ
- **Carbohydrates:** Commonly derived from grains like wheat, rice, and corn
- **Fat:** Commonly derived from animal fat, corn oil, and sunflower oil
- **Vitamins and minerals:** "Balanced" by the addition of purified or semipurified forms
- **Preservatives/Antioxidants:** Added to protect the food from oxidative damage. Either naturally derived or synthetic. Commonly used natural antioxidants include alpha-tocopherol and ascorbic acid. Synthetic forms include ethoxyquin and butylated hydroxytoluene (BHT).

When considering pet foods, attention must also be focused on the process of production. Health regulations require the cooking of pet food ingredients at temperatures intended to destroy any associated pathogenic microorganisms (Yeom et al., 2000; Gould, 2000); additionally, cooking enhances food palatability and digestibility. However these same temperatures are damaging to vital nutrients including enzymes, thiamin, folic acid, vitamin A, and niacin (Angelino et al., 1999; Reddy and Love, 1999; Severi et al., 1998; Yadav and Sehgal, 1997; Yadav and Sehgal, 1995; Dawson and Waters, 1994; Rumm-Kreuter and Demmel, 1990; Kimura et al., 1990; Skurikhin, 1985; Ranhotra et al., 1984; Smirnova et al., 1982; Head and Giesbrecht, 1976). During manufacturing of pet foods, starch is important for proper expansion of food pellets during extrusion. The temperature in the extruder can approach 150° C (Case et al., 2000, Harper, 1978). This is important because many proteins and enzymes are damaged or denatured at temperatures well below this (Kilara and Sharkasi, 1986). While additional starch improves food manufacturing, it contributes to what is now being recognized as carbohydrate overload.

Manufacturers overcome alterations in food constituents as a result of processing by adding purified and semipurified vitamins and minerals. These added components also serve as a way to increase key nutrients beyond the amounts present in commonly available food sources.

Synthetic Vitamins

Synthetic vitamins are chemically synthesized while isolated vitamins are modified from naturally occurring sources (Thiel, 2000). The physiological effects of synthetic vitamins are known to be different than vitamins from natural food sources (Lauridsen et al., 2002; Thiel, 2000; Hoppe and Krennrich, 2000; Patrick, 2000; Feskanich et al., 2000; Paisley, 1999; Burton et al., 1998; Lemoine and Le Devehat, 1989). Further, there are variations in the structure of synthetic vitamins and differences in their intestinal absorption, plasma and tissue kinetics, cellular uptake, and elimination (Thiel, 2000; Burton et al., 1998). It is assumed that because synthetic vitamins have close structural similarity to food source vitamins, they have the same physiological effects. However, the synthetic structure is not exactly the same as the natural vitamin, and thus the effects cannot be assumed to be exactly the same (Thiel, 2000; Sayama, 1991). As an example, natural alpha-tocopherol is a single stereoisomer (RRR) while synthetic alpha-tocopherol is an equimolar mixture of eight stereoisomers (all-racemic or *all-rac*). These forms are not chemically identical and vary in absorption, metabolism, and plasma and tissue kinetics (Thiel, 2000; Hoppe and Krennrich, 2000). In pigs, the bioactivity of RRR alpha-tocopherol was found to be greater than that of synthetic alpha-tocopherol acetates (Lauridsen et al., 2002). Synthetic alpha-tocopherol has been shown to be preferentially metabolized to its elimination product and more quickly excreted in urine (Traber et al., 1998). Synthetic alpha-tocopherol was also found to lower circulating lymphocyte levels (Goodwin and Garry 1983).

Use of synthetic or purified vitamins may result in a relative deficiency of the natural forms of these vitamins in the body (Thiel, 2000; Nakano et al., 1997; Ishida et al., 1994; Traber et al., 1993; Tandler et al., 1991). A synthetic vitamin and the resulting deficiency it causes affects the metabolism of the vitamin, as well as that of other nutrients. For example, in some animal species, synthetic vitamin A has been shown to alter vitamin E levels, whereas natural vitamin A does not. Lomnitski et al. (1991) showed that in the presence of vitamin E deficiency, isolated beta-carotene, in high concentrations, has a pro-oxidant effect *in vitro* and in animal studies. Additionally, while beta-carotene in foods has been correlated with reduced lung cancer incidence, recent studies suggest beta-carotene as an isolated supplement actually increases the risk of lung cancer in smokers (Paisley, 1999). The mechanism for this is unclear but may be related to nutrient imbalances created by the use of isolated beta-carotene.

There are numerous implications regarding the use of synthetic and isolated vitamins beyond those already pointed out. Metabolism and elimination of these xenobiotics requires the expenditure of energy and cellular resources, potentially leading to stressed metabolism in detoxification organs (Degkwitz, 1985; Bidlack and Smith, 1984). Primary sites of activity include the liver and kidney.

Efficient physiologic use of synthetic or isolated vitamins requires them to be combined with constituents normally present in the whole vitamin complex with which they act synergistically (Stahl et al., 1998; Staack et al., 1998). When these additional constituents are not consumed with the vitamin, they must be derived from nutrient storage sites in the body. Thus, continued ingestion of synthetic vitamins can lead to deficiencies of other essential nutritional factors and, in fact, reduce the ability of the body to utilize the synthetic vitamin (Thiel, 2000; Schelling et al., 1995). This is seen as a reduced therapeutic response, or even a worsening of the clinical condition, to synthetic vitamins following an initial benefit.

Synergism of Whole Foods

Because of synergy between substances found in whole foods, low concentrations of natural vitamins are found to have a significant physiological effect in contrast to the high concentrations of synthetic vitamins required to get a similar effect. This concept provides the foundation for the clinical effects of whole food concentrates.

The synergism that exists between the individual constituents of whole foods provides for a dynamic physiological response in which the benefits of the whole exceed the sum of the parts. In biological terms, this is seen as an increased therapeutic effect from much smaller quantities of nutrients. Therapeutically, synergy may also reduce side effects in treating health challenges (McPartland and Pruitt, 1999). Documentation shows this biological effect both in phytomedicines and whole foods (Williamson, 2001).

Synergistic interactions between individual constituents of a food are characterized by activity at low doses, with effects that exceed the predicted benefits of any isolated, single constituent (Staack et al., 1998; Stahl et al., 1998). These effects have been demonstrated *in vitro* for a variety of phytomedicines as well, including *Ginkgo biloba* (Chung et al., 1987; Wagner, 1999), *Piper methysticum* (Singh and Blumenthal, 1997), *Glycyrrhiza glabra* (Kimura et al., 1992), and *Zingiber officinalis* (Beckstrom-Sternberg and Duke, 1994), and in clinical situations evaluating phytomedicines and whole foods such as *Salix alba, Hypericum performatum, Panax* *ginseng,* ginkgo extract, *Valeriana officinalis*, and Brussels sprouts (Williamson, 2001; Staack et al., 1998).

Animal studies comparing the individual and collective effects of four Brussels sprout glucosinolate derivatives demonstrated a synergistic effect on induction of both Phase I and Phase II detoxification enzymes (Staack et al., 1998). Mixtures of carotenoids, especially those containing lutein and lycopene, have significantly better antioxidant potential *in vitro* than single, isolated carotenoids (Stahl et al., 1998). Studies such as these definitively illustrate functional synergy in whole foods.

Key Whole Foods

Individual whole foods may have increased concentrations of certain key whole vitamin complexes and associated synergistic factors that contribute to the support of specific organs and tissues. This support is the result of the whole food providing the proper balance of nutrients required by individual tissues. The following section highlights some food sources believed to have a particular benefit for the liver and heart. Although we focus only on these two structures here, other organs and glands are supported in a similar fashion by specific whole foods.

Liver

Nutritional support is a key factor in the treatment of hepatic disease in animals (Biourge, 1997). Nutritional goals for the management of hepatobiliary disease include:

- Maintenance of normal metabolic processes
- Avoiding accumulation of toxic metabolic wastes
- Providing nutritive substrates that support hepatic repair and regeneration

Support is mediated through the direct and indirect physiological effects of hepatic Protomorphogen™ extracts, whole food concentrates, and botanicals (Blackburn and O'Keefe, 1989).

Of primary importance in a hepatic support program is the inclusion of liver Protomorphogen™ extracts. These extracts are typically derived from fractionated bovine liver tissue and contain specific hepatocyte cell determinant factors that improve the local nutritional environment of the liver and support appropriate function of hepatocytes (Santoro and Weyhreter, 1993). Liver Protomorphogen™ extracts are beneficial for all cases of hepatic dysfunction and chronic degenerative disorders. Further, these extracts can be beneficial in cases of carbohydrate metabolism abnormalities, decreased serum albumin, ascites due to liver failure, renal disorders, and intestinal toxemia (Lee and Hanson, 1947).

The beneficial effects of hepatic Protomorphogen™ extracts are complemented by the vitamin complexes contained in such other whole food sources as lipid soluble chlorophyll extracts, rice bran concentrates, buckwheat concentrates, mushroom powder, Tillandsia powder, and alfalfa juice. These whole vitamin complexes enhance the ability of the liver to respond to metabolic demands while promoting its ability to heal and regenerate.

Concentrates from Strombus gigas (queen conch) provide a source of complete amino acids in a biological balance with trace minerals. The amino acids are needed to build various proteins used in growth, repair, and maintenance. It is also known that the conjugation of toxins for removal from the body utilizes the amino acids glutamine, ornithine, and glycine, prevalent in this whole food source. Providing amino acid substrates is especially important for optimal hepatic performance. Events in the liver related to protein regulation include amino acid storage and deamination for intermediary metabolism. Plasma amino acid profiles vary depending on the type of hepatic failure. In general, the essential amino acids (but not the branched-chain amino acids) and some of the nonessential amino acids are all degraded in the liver (Center, 1996; Strombeck and Rogers, 1978).

Liver and kidney concentrates provide a variety of nutrients and other valuable cell constituents for the liver. For example, vitamin A complex aids normal cellular reproduction and differentiation (Ross, 1993). This is beneficial not only for hepatocytes but also for all other liver-associated cells. Further, vitamin A is important for maintaining properly functioning cell membranes that are critical for preventing invasion by disease causing microorganisms (Navarro et al., 1990). High vitamin A intake increases microsomal metabolism of certain toxins (Anderson and Kappas, 1991). This is in addition to its other immune supportive functions.

Rice bran and yeast extracts provide a balance of the vitamin B complex. Components of the vitamin B complex are important for cell energy reactions that are mediated through enzymatic oxidative mechanisms related to carbohydrate metabolism. They play an important role in catalyzing various metabolic chain reactions through coenzymes and are indicated for poor muscle tone, cardiac problems, and improvement of intestinal motility (Gross et al., 2000). Adequate levels of thiamine are critical since a deficiency has been shown to strongly stimulate cytochrome P-450 activity and may potentiate hepatotoxicity caused by certain bioactivated intermediates (Yoo et al., 1990). Riboflavin deficiency ultimately leads to a decrease in the P-450 enzyme production and diminished Phase I monooxygenase activity (Wang et al., 1985).

Pantothenic acid is necessary for synthesis of Coenzyme A and thus may be important in avoiding damage from certain chemical toxins. Folic acid is a cofactor and methyl donor in Phase II conjugation pathways and aids homocysteine elimination. It also acts as a coenzyme in nucleotide biosynthesis and amino acid conversions (Jakoby et al., 1982). Folic acid deficiency can result in decreased methylation of DNA leading to chromosomal damage and potentially carcinogenesis (Rucker and Stites, 1994). Choline, found in a variety of foods including bovine liver and rice bran, is considered to be a structural element for cell membrane integrity and facilitates movement of lipids across cell membranes (Combs, 1992). Thus, choline is involved with many functions related to cellular phospholipids. Choline acts as a lipotrophic factor preventing the accumulation of lipids in the liver (Ghoshal and Farber, 1993). As a result, choline deficiency results in hepatic steatosis as well as hemorrhagic renal degeneration and depressed growth.

Buckwheat leaf and seed and mushroom powder provide bioflavonoids and the vitamin C complex, respectively (Duke, 2001). These nutrients have general benefits for healing and reducing inflammatory conditions. The bioflavonoids are useful for improvement of capillary fragility and promotion of normal arterial elasticity (Berger et al., 1992). Vitamin C complex is felt to aid in the formation of bile and certain detoxification processes. It also acts as an antioxidant. Vitamin C deficiency has been shown to impair oxidative drug metabolism and to reduce P-450 activity and associated enzymes (Jakoby et al., 1982).

Wheat germ oil is composed of almost 70% alpha-tocopherol, which is associated with other components of the whole vitamin E complex. Alpha-tocopherol is known to act as an antioxidant and, along with selenium, is a cofactor in glutathione peroxidase activity (Jakoby et al., 1982). It appears that vitamin E in cellular and subcellular membranes protects against phospholipid peroxidation. In addition, wheat germ oil has been shown to beneficially support certain endocrine glands like the adrenals (Azhar et al., 1995). Vitamin E deficiency combined with selenium deficiency has been implicated in cases of hepatic necrosis (Fraga et al., 1987).

Vitamin K complex is supplied by chlorophyll from alfalfa and beet leaf juice. It is essential for liver health since hepatic stores of vitamin K are limited and are rapidly depleted, especially when cholestasis or malabsorption exists. Patients with chronic hepatic disease frequently have abnormal blood coagulation and have been shown to respond to vitamin K administration (Center, 1996).

Trace minerals are important for proper hepatic function. One of these is zinc, which is an essential component in over 70 metalloenzymes. Therefore, zinc deficiency has a broad range of significant consequences (Jakoby et al., 1982). Copper is an integral part of superoxide dismutase, cytochrome oxidase, and amine oxidases, enzymes with antioxidant and detoxification activities. Copper is also required as a cofactor for the activity of catalases and peroxidases. Selenium is required for glutathione peroxidase activity.

In addition to the liver and kidney extracts, bovine liver fat extract is beneficial for liver health. Based on historical research, liver fat is believed to contain a hepatic “detoxifying hormone” known as Yakriton (Sato, 1927; Sato, 1928). By increasing liver blood flow, purification and detoxification of the blood may be enhanced. Thus, liver fat may be useful in cases of hepatic congestion.

Whole desiccated spleen is a source of superoxide dismutase, an antioxidant enzyme that acts on free radicals that interfere with normal cellular function (Freeman et al., 2000). Reduction of free radicals reduces their deleterious effects on cells (El-Sokkary et al., 2002). Further, the spleen is part of the lymphatic system and therefore contains immune tissue components. It can provide basic support for certain aspects of immune function and can benefit cases where inflammation is present or when blood cells are in need of support.

A number of botanical substances have been shown to have beneficial effects on liver function. One of these is Silybum marianum or milk thistle. It contains a bioflavonoid complex known as silymarin, which includes the compounds silibinin, silidianin, and silicristin. Silymarin protects liver cells by blocking entrance of harmful toxins through cell membranes.

These bioflavonoids also facilitate removal of toxins from liver cells (Hikino et al., 1984; Tuchweber et al., 1979), have antioxidant effects (Feher et al., 1986), regenerate injured liver cells (Sonnenbichler and Zetl, 1987), and are effective in humans with cirrhosis and chronic hepatitis (Ferenci et al., 1989). When combined with liver-damaging drugs, silymarin has been shown to protect the liver (Palasciano et al., 1994). There may be a stimulating effect on liver and gallbladder activity as well.

Taraxacum officinale (dandelion) root has been used to treat liver, gallbladder, digestion, kidney, and joint problems. The active factors include sesquiterpene lactones of the eudesmanolide and germacranolide type that are unique to the dandelion (Wichtl, 1994). Dandelion is also a rich source of vitamins and minerals, particularly beta-carotene, moderate vitamin D, vitamin C, various B vitamins, iron, silicon, magnesium, zinc, and manganese (Duke, 2001; Bradley, 1992). Dandelion stimulates digestion and increases bile production and flow. This may help improve fat metabolism and elmination of cholesterol. It should be noted that patients with biliary obstruction should avoid dandelion. Also dandelion may increase gastric acid production and should be used with caution in certain patients.

Ginkgo biloba has been shown to improve blood flow in small vessels. Its active components include ginkgo flavone glycosides and terpene lactones. These bioflavonoids have antioxidant properties. The terpene lactones are ginkgolides and bilobalide, which have been associated with increased blood circulation to the brain and other parts of body, as well as exerting a protective action on nerve cells (Bruno et al., 1993). These compounds also regenerate the tone and elasticity of blood vessels (Clostre, 1988) making circulation more efficient in both large vessels (arteries) and smaller vessels (capillaries). Further, *Ginkgo biloba* has been shown to exert direct antioxidant effects on the gastrointestinal mucosa and to improve gastrointestinal circulation.

Since the digestive tract plays an integral role in hepatic function, whole food ingredients specific for the gastrointestinal tract are useful. They provide a variety of structural and functional substrates. Stomach, duodenum, and jejunum extracts provide a range of complex substances including cell cytosol components. Black currant seed oil as a source of gamma-linolenic acid (GLA) can be beneficial for the integrity of the gut wall. GLA enhances production of prostaglandin E, which has been shown to reduce intestinal permeability and inflammation (Shah et al., 2001). Allantoin provides substances that promote general healing.

Heart

Multi-systemic and multiple tissue nutritional support for cardiac patients is best mediated through the administration of a variety of tissue concentrates and extracts, whole vitamin complexes, and botanicals selected for their benefits in supporting the biochemistry of the heart and related tissues. It has been the author's experience that afflicted patients can be maintained for extended periods with excellent quality of life in spite of significant heart disease. With appropriate nutritional therapy, patients thrive even in the face of poor prognostic indicators. The magnitude of the response is dependent on the quantity and viability of the remaining healthy cells. Therefore, early intervention is ideal. However, nutritional support is applicable at any time during the course of disease. Appropriate and timely monitoring allows for consistent adjustments in therapy for maximal benefits.

Heart Protomorphogen™ extracts have been shown to improve cardiac function by improving the local nutritional environment of the myocytes. In addition, there is an apparent benefit in reducing the damaging effects of the inflammatory process (Lee and Hanson, 1947). This is especially important in chronic cardiac conditions like cardiomyopathy in which ischemia is a prominent factor. It has been shown that post-ischemic damage is in part mediated by the inflammatory response (Entman et al., 1991). Heart Protomorphogen™ extracts have a variety of metabolic effects and can reduce the effects of any process that creates chronic injury to the myocardium.

Liver and kidney organ concentrates effectively deliver vital substances to their respective tissues. These substances can be critical in the process of replenishing depleted cellular supplies of key factors. Once these substances are replaced, cellular metabolism can begin to normalize. It is critical to recognize here that while many nutritional factors have been identified as beneficial for the liver and kidney, the myriad of essential substances needed for optimal function can only be speculated upon. Therefore, it is essential to utilize whole tissue extracts to provide both known and unknown substances in their physiologically active forms. Recognition of the need to support these tissues is important because of the central role that they play in the metabolic processes of the body, particularly cardiac function.

Spleen concentrates are known to contain high levels of superoxide dismutase, which has been shown to reduce the damaging effects of hypoxia on the myocardium by acting as a free radical scavenger (Itoh et al., 1999).

The benefits of tissue Protomorphogen™ extracts and tissue concentrates can be maximized by the addition of whole vitamin complexes derived from food sources. These sources include rice bran, pea vine, wheat germ, alfalfa, flaxseed oil, buckwheat, mushroom, and beet root. Additional supportive benefits can be provided by botanicals like *Crataegus laevigata* and *Emblica officinalis*, which are known to exert positive supportive effects on the heart.

Rice bran is considered an excellent source of lipids, protein, vitamin B complex, inositol, and choline (Duke, 2001; Ogawa, 1999; Jariwalla, 2001). This is in addition to the antioxidants it contains, including vitamin E, ferulic acid, and oryzanols (Osawa, 1999). These food factors have been shown to have direct and indirect effects on the heart (Jariwalla, 2001). Vitamin B complex factors are thought to be beneficial in "coordinating" nerve control of the heart with muscular contraction. Myoinositol in rice bran is an important cell membrane phospholipid that was first discovered in heart muscle (Ogawa, 1999). It also has the benefit of being lipotrophic, reducing the accumulation of fat in the liver (Katayama, 1999), and this offers supportive effects for the liver that can assist in maintaining appropriate liver function. Choline is a precursor to the neurotransmitter acetylcholine as well as phosphatidylcholine and sphingomyelin, cell membrane phospholipids (Blusztajn, 1998). Choline is lipotrophic and can be oxidized to form betaine (Zeisel, 1992). It facilitates folate metabolism (Landgren et al., 1995) and increases the conversion of homocysteine to methionine (Alonso-Aperte and Varela-Moreiras, 1996). While an elevated homocysteine level has not been proven as a risk factor for heart disease in veterinary medicine, this has been shown for humans and *in vitro* studies have demonstrated an injurious effect on animal endothelial cells (Wall et al., 1980).

Beet (*Beta vulgaris*) root contains betaine (Weretilnyk et al., 2001), glutamine (Mack, 1998), high levels of folic acid (Wang and Goldman, 1997), and triterpene saponins (Massiot et al., 1994). Betaine is an important methyl group donor that participates in the conversion of homocysteine to methionine (Selhub, 1999; Maree et al., 1990) and facilitates Phase II hepatic detoxification (McKevoy, 1998).

Alfalfa provides a source of bioavailable protein, vitamin A, C, E, and K complexes, carotenoids, chlorophyll, calcium, potassium, phosphorus, isoflavonoids, and triterpene saponins (Duke, 2001). Each of these factors provides direct and indirect benefits for the heart. For example, alfalfa derived isoflavonoids act to improve the health of the cardiovascular system (Kurzer and Xu, 1997). Indirect benefits are mediated through mineral-induced relaxation of the autonomic nervous system and chlorophyll complexing of toxins (Sarkar et al., 1994).

Pea vine juice has a unique vitamin E complex composition. Components of the vitamin E complex have been shown to have an antioxidant effect that is protective for nutrients such as vitamin A and vitamin B complex while they are still in the lumen of the digestive tract. In addition to its other antioxidant effects, vitamin E promotes normal coronary artery dilation (Emmert and Kirchner, 1999). Studies investigating the cardiac benefits of alpha-tocopherol have found that it reduced the incidence and severity of heart disease (Freeman et al., 1999), prevented a decrease in myocardial contraction induced by volume overload (Prasad et al., 1996), prevented the occurrence of lethal ventricular arrhythmias associated with ischemia and reperfusion (Sebbag et al., 1994), and reduced infarct size in experimental ischemia reperfusion in dogs (Tripathi and Hedge, 1997). Reports from vitamin E deficiency studies indicate a variety of cardiac manifestations depending on the animal species under investigation. These manifestations include gross and histological changes in the myocardium (Bragdon and Levine, 1949; Houchin and Smith, 1944; Mason and Telford, 1947) and ECG abnormalities (Gullickson and Calverley, 1946; Filer et al., 1949; Dinning et al., 1951; Ensor, 1946). The essential point gleaned from investigations of vitamin E is that it has been shown to have a supportive role in maintaining cardiac health. However, it is critical to recognize the differences between the vitamin E complex, which contains multiple tocopherols, selenium, and other factors, and alpha-tocopherol as an isolated synthetic vitamin, which is quite limited in function.

Buckwheat (*Fagopyrum spp.*) is known to contain significant amounts of common flavonoids like quercetin and rutin (Quettier-Deleu et al., 2000; Dietrych-Szostak and Oleszek, 1999), as well as numerous antioxidants and a favorable amino acid composition (Tomotake et al., 2000; Li and Zhang, 2001). It is a major source of building blocks and supportive nutrients for the heart muscle and other vascular structures.

Conclusion

Whole foods provide superior nutrition for preventing disease and giving support during illness. Their whole vitamin complexes facilitate the physiological effects of whole foods far better than synthetic isolates. Interestingly, whole vitamin complexes have physiological effects that are far greater than would be expected from the additive effects of their individual components. This enhanced effect is based on synergistic interactions between whole foods and their whole vitamin complex factors. This synergism occurs through the unique combination of constituents within a whole food.

It is important to contrast this with the synthetic vitamin that does not have the necessary accompanying cofactors to manifest a synergistic response. Factors associated with the whole vitamin complex that contribute to the synergistic effect include enzymes, coenzymes, trace minerals, and antioxidants. Without this critical synergy, synthetic vitamins must be delivered in higher (supraphysiological) doses to achieve comparable results. For example, some estimates have suggested natural alpha-tocopherol may be twice as bioavailable as its synthetic counterpart (Thiel, 2000; Burton et al., 1998). Other factors that affect the physiological effects of synthetic vitamins include the health of the digestive tract, body stores of synergistic factors, metabolism, and the rate of elimination. Multiple digestive conditions influence the absorption of both whole vitamin complexes and synthetic vitamins. Therefore, plasma concentrations after ingestion can be variable.

Speculation based on feeding studies with synthetic vitamins leads to the conclusion that synthetic vitamins may require some degree of reassembly following absorption as the body tries to convert them to biologically useful forms. Via this reassembly, the synthetic vitamin becomes associated with a variable number of factors that are normally part of the whole vitamin complex needed for function. However, these additional components must be derived from the body's endogenous stores since they are not present with the synthetic vitamin. The implications are multifold and include diversion of important components away from other normal biochemical pathways and potential depletion of body stores of these factors, leading to a relative deficiency and reduced response to the synthetic vitamin, as has been suggested (Thiel, 2000).

Synthetic vitamins are added to most commercial pet foods and can be classified as xenobiotics. The body must eliminate these chemicals, which are perceived as foreign. Elimination occurs through hepatobiliary and renal routes. Preferential elimination has been demonstrated for some synthetic vitamins (Hoppe and Krennrich, 2000; Habash et al., 1999; Traber et al., 1998). Obviously, elimination of these xenobiotics requires metabolic processes that utilize cellular constituents. This creates cellular metabolic stresses that, generally, are appropriately managed. However, it has the potential to further compromise an already diseased and/or nutritionally depleted organ. This reduces the ability of the tissue to heal and regenerate.

Commercial pet food production results in foods that are over processed with the result that nutrients are damaged and destroyed. Synthetic vitamins and other substances are added in an effort to compensate for this nutrient loss. However, these additives create ongoing metabolic stresses that coupled with the limited ingredient selection and processing of foods leads to situations in which cellular nutritional status can be compromised, causing tissue malnutrition.

Effective nutritional support for patients requires an understanding of the physiological needs of the diseased tissues in conjunction with insight into the normal metabolic processes of those tissues. Further, this nutritional support is best provided with products that provide whole foods and whole vitamin complexes that are derived from a variety of natural sources and that appropriately match the requirements of that animal species. Whole food nutritional supplements can be utilized to support already diseased patients and to compensate for nutritional situations that may occur as a result of chronically ingesting commercial, processed pet foods containing synthetic vitamins. Nutritional supplementation should be patient specific based on individual needs and predispositions. These needs are recognized based on the patient condition, history, breed, and species.

References

Alonso-Aperte, E. and G. Varela-Moreiras. 1996. Brain folates and DNA methylation in rats fed a choline deficient diet or treated with low doses of methotrexate. Int J *Vitam Nutr Res* 66(3): 232-236.

Anderson, K. E. and A. Kappas. 1991. Dietary regulation of cytochrome P-450. *Ann Rev Nutr* 11: 141-167.

Angelino, P. D. et al. 1999. Residual alkaline phosphatase activity in pasteurized milk heated at various temperatures—measurement with the fluorophos and Scharer rapid phosphatase tests. *J Food Prot* 62(1): 81-85.

Azhar, S. et al. 1995. Alteration of the adrenal antioxidant defense system during aging in rats. *J Clin Invest* 96(3): 1414-1424.

Barnes, P. J. 1982. Composition of cereal germ preparations. *Z Lebensm Unters Forsch* 174(6): 467-471.

Barnes, P. J. and P. W. Taylor. 1980. The composition of acyl lipids and tocopherols in wheat germ oils from various sources. *J Sci Food Agric* 31(10): 997-1006.

Barnett, K. C. and I. H. Burger. 1980. Taurine deficiency retinopathy in the cat. *J Small Anim Pract* 21(10): 521-534.

Beckstrom-Sternberg, S. M. and J. A. Duke. 1994. Potential for synergistic action of phytochemicals in spices. *In: Charalambous*, G. (ed.). Spices, herbs and edible fungi. Amsterdam: Elsevier. 210-233.

Berger, M. E. et al. 1992. Flavonoid potentiation of contractile responses in rat blood vessels. *J Pharmacol Exp Ther* 263(1): 78-83.

Bidlack, W. R. and C. H. Smith. 1984. The effect of nutritional factors on hepatic drug and toxicant metabolism. *J Am Diet Assoc* 84(8): 892-898.

Biourge, V. C. 1997. Nutrition and liver disease. *Semin Vet Med Surg* (Small Anim) 12(1): 34-44.

Blackburn, G. L. and S. J. D. O'Keefe. 1989. Nutrition in liver failure. *Gastroenterology* 97: 1049-1051.

Blusztajn, J. K. 1998. Choline, a vital amine. *Science* 281(5378): 794-795.

Bousvaros, A. et al. 1998. Vitamins A and E serum levels in children and young adults with inflammatory bowel disease: Effect of disease activity. *J Pediatr Gastroenterol Nutr* 26(2): 129-135.

Bradley, P. R. (ed). 1992. *British Herbal Compendium*, Vol 1. Bournemouth, Dorset, UK: British Herbal Medicine Association. 73-75.

Bragdon, J. H. and H. D. Levine. 1949. Myocarditis in vitamin E deficient rabbits. *Amer J Path* 25: 265.

Brown, R. G. 1994. Understanding advertising in pet nutrition. *Can Vet J* 35(4): 246-250.

Bruno, C. et al. 1993. Regeneration of motor nerves in bilobalide-treated rats. *Planta Medica* 59: 302-307.

Burton, G. W. et al. 1998. Human plasma and tissue alpha-tocopherol concentrations in response to supplementation with deuterated natural and synthetic vitamin E. *Am J Clin Nutr* 67(4): 669-684.

Calder, P. C. 2001. Polyunsaturated fatty acids, inflammation, and immunity. *Lipids* 36(9): 1007-1024.

Carpenter, K. J. and B. Sutherland. 1995. Eijkman's contribution to the discovery of vitamins. *J Nutr* 125(2): 155-163.

Case L.P. et .al. 2000. *Canine and feline nutrition*. A resource for companion animal professionals, 2nd ed. Philadelphia, PA: Mosby. 178.

Center, S. A. 1996. Pathophysiology of liver disease: Normal and abnormal function. In: Guilford, W. G. et al. (eds). *Strombeck's Small Animal Gastroenterology*, 3rd ed. Philadelphia, PA: WB Saunders Co. 553-632.

Chung, K. F. et al. 1987. Effect of a ginkgolide mixture (BN 52063) in antagonising skin and platelet responses to platelet activating factor in man. *Lancet* 1(8527): 248-251.

Clausen, T. and I. Dorup. 1998. Micronutrients, minerals and growth control. *Bibl Nutr Dieta* 54: 84-92.

Clostre, F. 1988. From the body to the cellular membranes: The different levels of pharmacological action of *Ginkgo biloba* extract. In: Funfgeld, E. W. (ed). Rokan (*Ginkgo biloba*): Recent results in pharmacology and clinic. Berlin: Springer-Verlag. 180-198.

Combs, G. F. (ed). 1992. The vitamins, fundamental aspects of nutrition and health. San Diego, CA: Academic Press, Inc.

Dawson, D. W. and H. M. Waters. 1994. Malnutrition: folate and cobalamin deficiency. *Br J Biomed Sci* 51(3): 221-227.

Degkwitz, E. 1985. New aspects of the biochemistry of vitamin C. *Z Ernahrungswiss* 24(4): 219-230.

Dietrych-Szostak, D. ans W. Oleszek. 1999. Effect of processing on the flavonoid content of buckwheat (Fagopyrum esculentum Moench) grain. *J Agric Food Chem* 47: 4384-4387.

Dinning, J. S. et al. 1951. Acute vitamin E deficiency in the monkey. *Fed Proc* 10: 380.

Duke, J. A. 2001. *Handbook of phytochemical constituents of GRAS herbs and other economic plants.* Boca Raton, FL: CRC Press LLC. 364-366.

Dzanis, D. A. 1998. Regulatory aspects of diets, supplements, and nutraceuticals. *Clin Tech Small Anim Pract* 13(4): 193-196.

El-Sokkary, G. H. et al. 2002. Melatonin reduces oxidative damage and increases survival of mice infected with Schistosoma mansoni. *Free Radic Biol Med* 32(4): 319-332.

Emmert, D. H. and J. T. Kirchner. 1999. The role of vitamin E in the prevention of heart disease. *Arch Fam Med* 8(6): 537-542.

Ensor, C. R. 1946. The electrocardiogram of rats in vitamin E deficiency. *Amer J Physiol* 147: 242.

Entman, M. L. et al. 1991. Inflammation in the course of early myocardial ischemia. *FASEB J* 5(11): 2529-2537.

Feher, J. et al. 1986. Free radicals in tissue damage in liver diseases and therapeutic approach. *Tokai J Exp Clin Med* 11(Suppl): 121-134.

Ferenci, P. et al. 1989. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 9: 105-113.

Feskanich, D. et al. 2000. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *J Natl Cancer Inst* 92(22): 1812-1823.

Filer, L. J. et al. 1949. Studies on vitamin E deficiency in the monkey. *Ann New York Acad Sci* 52: 284.

Firth, M. and E. Marvan. 2001. Oral lesions in scurvy. *Aust Dent J* 46(4): 298-300.

Fraga, C. G. et al. 1987. Effect of vitamin E- and selenium-deficiency on rat liver chemiluminescence. *Biochem J* 242(2): 383-386.

Freeman, B. D. et al. 2000. Role of CuZn superoxide dismutase in regulating lymphocyte apoptosis during sepsis. *Crit Care Med* 28(6): 1701-1708.

Freeman, L. M. 1998. Interventional nutrition for cardiac disease. *Clin Tech Small Anim Pract* 13(4): 232-237.

Freeman, L. M. et al. 1999. Assessment of degree of oxidative stress and antioxidant concentrations in dogs with idiopathic dilated cardiomyopathy. *J Am Vet Med Assoc* 215(5): 644-646.

Frick, J. et al. 1994. Yield and seed oil content response of dwarf, rapid-cycling Brassica to nitrogen treatments, planting density, and carbon dioxide enrichment. *J Am Soc Hortic Sci* 119(6): 1137-1143.

Ghebremeskel, K. and M. A. Crawford. 1994. Nutrition and health in relation to food production and processing. *Nutr Health* 9(4): 237-253.

Ghoshal, A. K. and E. Farber. 1993. Choline deficiency, lipotrope deficiency and the development of liver disease including liver cancer: A new perspective. *Lab Invest* 68(3): 255-260.

Goodwin, J. S. and P. G. Garry. 1983. Relationship between megadose vitamin supplementation and immunological function in a healthy elderly population. *Clin Exp Immunol* 51(3): 647-653.

Gould, G. W. 2000. Preservation: Past, present and future. *Br Med Bull* 56(1): 84-96.

Gross, K. L. et al. 2000. Nutrients. In: Hand, M. S. et al. (eds). *Small Animal Clinical Nutrition*, 4th ed. Marceline, MO: Walsworth Publishing Co. 82-83.

Gullickson, T. W. and C. E. Calverley. 1946. Cardiac failure in cattle on vitamin E-free rations as revealed by electrocardiograms. *Science* 104: 312.

Gwazdauskas, F. C. et al. 1986. Adrenal response during periparturient period to adrenocorticotropin in dairy cattle fed corn silage and grass legume silage. *J Dairy Sci* 69(8): 2134-2139.

Habash, M. B. et al. 1999. The effect of water, ascorbic acid, and cranberry derived supplementation on human urine and uropathogen adhesion to silicone rubber. *Can J Microbiol* 45(8): 691-694.

Harper, J. M. 1978. Food extrusion. CRC *Crit Rev Food Sci Nutr* 11(2): 155-215.

Hayes, K. C. et al. 1975. Retinal degeneration associated with taurine deficiency in the cat. *Science* 188(4191): 949-951.

Head, M. K. and F. G. Giesbrecht. 1976. Effects of storage and handling on vitamins in fresh lima beans. *J Am Diet Assoc* 69(6): 640-644.

Hermus, R. J. and A. H. Severs. 1999. Clinical significance of extra vitamin supplements and enriched food products. *Ned Tijdschr Geneeskd* 143(17): 889-893.

Hikino, H. et al. 1984. Antihepatotoxic action of flavonolignans from *Silybum marianum* fruits. *Planta Medica* 50: 248-250.

Hoppe, P. P. and G. Krennrich. 2000. Bioavailability and potency of natural-source and all-racemic alpha-tocopherol in the human: A dispute. *Eur J Nutr* 39(5): 183-193.

Houchin, O. B. and P. W. Smith. 1944. Cardiac insufficiency in the vitamin E deficient rabbit. *Am J Physiol* 141: 242.

Huber, T. L. et al. 1986. Variations in digestibility of dry dog foods with identical label guaranteed analysis. *J Am Anim Hosp Assoc* 22: 571-575.

Huber, T. L. et al. 1991. Comparison of procedures for assessing adequacy of dog foods. *J Am Vet Med Assoc* 199(6): 731-734.

Ishida, A. et al. 1994. Microbiological activities of nucleotide loop-modified analogues of vitamin B12. *Arch Microbiol* 161(4): 293-299.

Ishikawa, Y. 2000. Niacin deficiency disease (pellagra). *Ryoikibetsu Shokogun Shirizu* 29(4): 91-93.

Itoh, S. et al. 1999. Generation of free radicals and the damage done to the sarcoplasmic reticulum during reperfusion injury following brief ischemia in the canine heart. *Jpn Circ J* 63(5): 373-378.

Ivanova, T. N. et al. 1993. The first "space" vegetables have been grown in the "SVET" greenhouse using controlled environmental conditions. *Acta Astronaut* 29(8): 639-644.

Jacob, F. et al. 2002. Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs. *JAVMA* 220: 1163-1170.

Jakoby, W. B. et al. (eds). 1982. *Metabolic basis of detoxification: Metabolism of functional groups*. New York: Academic Press, Inc.

Jariwalla, R. J. 2001. Rice-bran products: Phytonutrients with potential applications in preventive and clinical medicine. *Drugs Exp Clin Res* 27(1): 17-26.

Kallfelz, F. A. 1989. Evaluation and use of pet foods: General considerations in using pet foods for adult maintenance. *Vet Clin North Am Small Anim Pract* 19(3): 387-402.

Katayama, T. 1999. Hypolipidemic action of phytic acid (IP6): Prevention of fatty liver. Anticancer Res 19(5A): 3695-3698.

Kato, M. et al. 1984. Immunocytochemical studies on the localization of plasma and of cellular retinol-binding proteins and of transthyretin (prealbumin) in rat liver and kidney. *J Cell Biol* 98(5): 1696-1704.

Keicher, U. et al. 1995. Omega-3 fatty acids suppress the enhanced production of 5-lipoxygenase products from polymorph neutrophil granulocytes in cystic fibrosis. *Eur J Clin Invest* 25(12): 915-919.

Kilara, A. and T. Y. Sharkasi. 1986. Effects of temperature on food proteins and its implications on functional properties. *Crit Rev Food Sci Nutr* 23(4): 323-395.

Kimura, M. et al. 1990. Cooking losses of thiamin in food and its nutritional significance. *J Nutr Sci Vitaminol* (Tokyo) 36(Suppl 1): S17-S24.

Kimura, M. et al. 1992. Combined effects of Japanese-Sino medicine "Kakkon-to-ka-senkyu-shin'I" and its related combinations and component drugs on adjuvant-induced inflammation in mice. *Phytother Res* 6(4): 209-216.

King, J. C. 2002. Biotechnology: A solution for improving nutrient bioavailability. *Int J Vitam Nutr Res* 72(1): 7-12.

Kurilich, A. C. et al. 1999. Carotene, tocopherol, and ascorbate contents in subspecies of Brassica oleracea. *J Agric Food Chem* 47(4): 1576-1581

Kurzer, M. S. and X. Xu. 1997. Dietary phytoestrogens. *Annu Rev Nutr* 17: 353-381.

Kushad, M. M. et al. 1999. Variation of glucosinolates in vegetable crops of Brassica oleracea. *J Agric Food Chem* 47(4): 1541-1548.

Landgren, F et al. 1995. Plasma homocysteine in acute myocardial infarction: Homocysteine-lowering effect folic acid. *J Intern Med* 237(4): 381-388.

Lauridsen, C. et al. 2002. Relative bioactivity of dietary RRR- and all-rac-alpha-tocopheryl acetates in swine assessed with deuterium-labeled vitamin E. *J Anim Sci* 80(3): 702-707.

Lee, R. and W. A. Hanson. 1947. *Protomorphology: The Principles of Cell Auto-regulation*. Milwaukee, WI: Lee Foundation.

Lekcharoensuk, C. et al. 2002. Associations between dietary factors in canned food and formation of calcium oxalate uroliths in dogs. *Am J Vet Res* 63(2): 163-169.

Leklem, J. E. et al. 1980. Bioavailability of vitamin B-6 from wheat bread in humans. *J Nutr* 110(9): 1819-1828.

Lemoine, A. and C. Le Devehat. 1989. Clinical conditions requiring elevated dosages of vitamins. *Int J Vitam Nutr Res Suppl* 30: 129-147.

Leonardi, C. et al. 2000. Antioxidative activity and carotenoid and tomatine contents in different typologies of fresh consumption tomatoes. *J Agric Food Chem* 48(10): 4723-4727.

Lessell, S. 1998. Nutritional amblyopia. *J Neuroophthalmol* 18(2): 106-111.

Li, S. Q. and Q. H. Zhang. 2001. Advances in development of functional foods from buckwheat. *Crit Rev Food Sci Nutr* 41(6): 451-464.

Lindberg, A. S. et al. 1983. The effect of wheat bran on the bioavailability of vitamin B-6 in young men. *J Nutr* 113(12): 2578-2586.

Loerch, S. C. and F. L. Fluharty. 1999. Physiological changes and digestive capabilities of newly received feedlot cattle. *J Anim Sci* 77(5): 1113-1119.

Lomnitski, L. et al. 1991. The effect of dietary vitamin E and beta-carotene on oxidation processes in the rat testis. *Biochim Biophys Acta* 1082(1): 101-107.

Mack, G. 1998. Glutamine synthetase isoenzymes, oligomers and subunits from hairy roots of Beta vulgaris L. var. lutea. *Planta* 205(1): 113-120.

Malfait, P. et al. 1993. An outbreak of pellagra related to changes in dietary niacin among Mozambican refugees in Malawi. *Int J Epidemiol* 22(3): 504-511.

Maree, K. A. et al. 1990. Interrelationship between serum concentrations of methionine, vitamin B12 and folate. *Int J Vitam Nutr Res* 60(2): 136-141.

Mason, K. E. and I. R. Telford. 1947. Some manifestations of vitamin E deficiency in the monkey. *Arch Path* 43: 363.

Massiot, G. et al. 1994. Seco-glycosides of oleanolic acid from Beta vulgaris. *Phytochemistry* 37(6): 1667-1670.

McKeehen, J. D. et al. 1996. Effect of CO2 levels on nutrient content of lettuce and radish. *Adv Space Res* 18(4-5): 85-92.

McKevoy, G. K. (ed). 1998. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists.

McPartland, J. M. and P. L. Pruitt. 1999. Side effects of pharmaceuticals not elicited by comparable herbal medicines: The case of tetrahydrocannabinol and marijuana. *Alternative Therapies* 5(4): 57-62.

Mikkonen, T. P et al. 2001. Flavonol content varies among black currant cultivars. *J Agric Food Chem* 49(7): 3274-3277.

Morris, J. G. and Q. R. Rogers. 1994. Assessment of the nutritional adequacy of pet foods through the life cycle. *J Nutr* 124(12 Suppl): 2520S-2534S.

Nakano, H. et al. 1997. Pyridoxine-5'-beta-glucoside exhibits incomplete bioavailability as a source of vitamin B-6 and partially inhibits the utilization of co-ingested pyridoxine in humans. *J Nutr* 127(8): 1508-1513.

Navarro, E. E. et al. 1990. Clinicopathologic studies of children who die of acute lower respiratory tract infections: Mechanisms of death. *Rev Infect Dis* 12(Suppl 8): S1065-S1073.

Ogawa, S. 1999. Chemical components of rice bran: Myo-inositol and related compounds: A review. *Anticancer Res* 19: 3635-3644.

Ogilvie, G. K. 1998. Interventional nutrition for the cancer patient. *Clin Tech Small Anim Pract* 13(4): 224-231.

Osawa, T. 1999. Protective role of rice polyphenols in oxidative stress. *Anticancer Res* 19: 3645-3650.

Paisley, J. A. 1999. Beta-Carotene and Lung Cancer: A Review of Randomized Clinical Trials. *Can J Diet Pract Res* 60(3): 160-165.

Palasciano, G. et al. 1994. The effect of silymarin on plasma levels of malondialdehyde in patients receiving long-term treatment of psychotropic drugs. *Curr Ther Res* S5: S37-S45.

Patrick, L. 2000. Beta-carotene: The controversy continues. *Altern Med Rev* 5(6): 530-545.

Pautas, E. et al. 1999. Vitamin B 12 deficiency in the aged. *Presse Med* 28(32): 1767-1770.

Pedersen, N. C. 1992. Inflammatory oral cavity diseases of the cat. *Vet Clin North Am Small Anim Pract* 22(6): 1323-1345.

Phillips, W. A. et al. 1982. Influence of preshipment management on the adrenal response of beef calves to ACTH before and after transit. *J Anim Sci* 54(4): 697-703.

Pion, P. D. et al. 1987. Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. *Science*. 237(4816): 764-768.

Plopper, C. G. et al. 1977. Autoradiographic localization of vitamin A in the kidney of rats. *Proc Soc Exp Biol Med* 155(1): 124-127.

Pottenger, E. and R. T. Pottenger (eds.). 1995. *Pottenger's Cats: A Study in Nutrition,* 2nd Ed. La Mesa, CA: Price-Pottenger Nutrition Foundation.

Prasad, K. et al. 1996. Oxidative stress as a mechanism of cardiac failure in chronic volume overload in canine model. *J Mol Cell Cardiol* 28(2): 375-385.

Premuzic, Z. et al., 1998. Calcium, iron, potassium, phosphorus and vitamin C content of organic and hydroponic tomatoes. *Hort Science* 33(2): 255-257.

Price, W. A. 1945, 1997. *Nutrition and Physical Degeneration*, 6th Ed. La Mesa, CA: Price-Pottenger Nutrition Foundation.

Quettier-Deleu, C. et al. 2000. Phenolic compounds and antioxidant activities of buckwheat (Fagopyrum esculentum Moench) hulls and flour. *J Ethnopharmacol* 72(1-2): 35-42.

Rajakumar, K. 2001. Infantile scurvy: A historical perspective. *Pediatrics* 108(4): E76.

Ranhotra, G. S. et al. 1984. Nutritive value of selected variety breads and pastas. *J Am Diet Assoc* 84(3): 322-327.

Rao, B. S. N. 2000. Nutritive value of rice bran. *NFI Bulletin* 21(4): 5-8.

Reddy, M. B. and M. Love. 1999. The impact of food processing on the nutritional quality of vitamins and minerals. *Adv Exp Med Biol* 459: 99-106.

Reotutar, R. 1989. Pet food makers found guilty of false advertisement claims. *J Am Vet Med Assoc*. 1989 Oct 1;195(7):873

Reus, K. E. et al. 2000. Food additives as a cause of medical symptoms: Relationship shown between sulfites and asthma and anaphylaxis; results of a literature review. *Ned Tijdschr Geneeskd* 144(38): 1836-1839.

Romero Rodriguez, M. A. et al. 1992. Determination of vitamin C and organic acids in various fruits by HPLC. *J Chromatogr Sci* 30(11): 433-437.

Ross, A. C. 1993. Cellular metabolism and activation of retinoids: Roles of cellular retinoid-binding proteins. *FASEB J* 7(2): 317-327.

Rucker, R. B. and T. Stites. 1994. New perspectives on function of vitamins. *Nutrition* 10(6): 507-513.

Rumm-Kreuter, D. and I. Demmel. 1990. Comparison of vitamin losses in vegetables due to various cooking methods. *J Nutr Sci Vitaminol* (Tokyo). 36(Suppl 1):S7-S14;

discussion S14-15.
Sadiq, M. and W. A. Abdurrehman. 1999. Elemental composition of alfalfa leaves and its relation to soil composition and irrigation water quality in the Eastern Province of Saudi Arabia. *J Plant Nutr* 22(8): 1269-1278.
Santoro, R. L. and A. F. Weyhreter. 1993. Support of human gland.organ function with raw protein concentrate as measured by improvement in serum chemistry values. *J Appl Nutr* 45(2): 48-60.
Sarkar, D. et al. 1994. Chlorophyll and chlorophyllin modifiers of genotoxic effects. *Mutat Res* 318(3): 239-247.
Sato, A. 1927. Studies on the detoxicating hormone of the liver (yakriton): 4th Report. *Tohoku J Exp Med* 8: 351-354.
Sato, A. 1928. Studies on the detoxicating hormone of the liver (yakriton): 7th Report. *Tohoku J Exp Med* 11: 272-276.
Sayama, T. 1991. Vitamin E in foods (tocopherol) natural or synthetic. *Euro Food Drink Rev* Winter: 15-17, 19.
Scanlan, N. 2001. Compromised hepatic detoxification in companion animals and its correction via nutritional supplementation and modified fasting. *Altern Med Rev* 6(Suppl): S24-S37.
Schroeder, H. A. 1971. Losses of vitamins and trace minerals resulting from processing and preservation of foods. *Am J Clin Nutr* 24(5): 562-573.
Sebbag, L. et al. 1994. Effects of dietary supplementation of alpha-tocopherol on myocardial infarct size and ventricular arrhythmias in a dog model of ischemia and reperfusion. *J Am Cell Cardiol* 24: 1580-1585.
Selhub, J. 1999. Homocysteine metabolism. *Annu Rev Nutr* 19: 217-246.
Selhub, J. et al. 2000. B vitamins, homocysteine, and neurocognitive function in the elderly. *Am J Clin Nutr* 71(2): 614S-620S.
Severi, S. et al. 1998. Effects of home-based food preparation practices on the micronutrient content of foods. *Eur J Cancer Prev* 7(4): 331-335.
Shah, A. A. et al. 2001. Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: A comparison of nimesulide and naproxen. *Gut* 48(3): 339-346.
Shirahata, A. 1999. Hepatobiliary and pancreatic disorders as risk factors for fat-soluble vitamin deficiencies. *Nippon Rinsho* 57(10): 2371-2375.
Singh, Y. N. and M. Blumenthal. 1997. Kava. An Overview. *Herbalgram* 39: 33-56.
Skurikhin, I. M. 1985. Changes in the nutritive value of food products after thermal culinary handling. *Vopr Pitan* (2): 66-69.
Smirnova, L. V. et al. 1982. Vitamin content in groats before and after technological processing. *Vopr Pitan* (2): 62-63.
Smith, J. E. et al. 1975. Tissue distribution and subcellular localization of retinol-binding protein in normal and vitamin A-deficient rats. *J Lipid Res* 16(4): 318-323.
Sonnenbichler, J. and I. Zetl. 1987. Stimulating influence of a flavonolignan derivative on proliferation, RNA synthesis and protein synthesis in liver cells. In: Okolicsanyi, L. et al. (eds). Assessment and Management of Hepatobiliary Disease. Berlin: Springer-Verlag. 265-272.
Sousa, C. A. et al. 1988. Dermatosis associated with feeding generic dog food: 13 cases (1981-1982). *J Am Vet Med Assoc* 192(5): 676-680.
Staack, R. et al. 1998. A comparison of the individual and collective effects of four glucosinolate breakdown products from Brussels sprouts on induction of detoxification enzymes. *Tox Appl Pharm* 149: 17-23.
Stahl, W. et al. 1998. Carotenoid mixtures protect multilamellar liposomes against oxidative damage: Synergistic effects of lycopene and lutein. *FEBS Lett* 427(2): 305-308.
Strombeck, D. R. and Q. R. Rogers. 1978. Plasma amino acid concentrations in dogs with hepatic disease. *J Am Vet Med Ass* 173: 93-96.
Sundrum, A. et al. 2000. Effects of on-farm diets for organic pig production on performance and carcass quality. *J Anim Sci* 78(5): 1199-1205.
Swanson, J. M. and M. Kinsbourne. 1980. Food dyes impair performance of hyperactive children on a laboratory learning test. *Science* 207(4438): 1485-1487.
Tallaksen, C. M. and G. Bovim. 1998. Thiamine treatment today. *Tidsskr Nor Laegeforen* 118(25): 3946-3949.
Tandler, B. et al. 1991. Unusual mitochondria in the hepatocytes of rats treated with a vitamin B12 analogue. *Anat Rec* 231(1): 1-6.
Thiel, R. J. 2000. Natural vitamins may be superior to synthetic ones. *Med Hypotheses* 55(6): 461-469.
Tomotake, H. et al. 2000. A buckwheat protein product suppresses gallstone formation and plasma cholesterol more strongly than soy protein isolate in hamsters. *J Nutr* 130(7): 1670-1674.
Townsend, M. S. et al. 1999. Differential concentration of ten minerals among four ancestral alfalfa germplasms. *Crop Sci* 39(2): 574-578.
Traber, M. G. et al. 1993. Impaired discrimination between stereoisomers of alpha-tocopherol in patients with familial isolated vitamin E deficiency. *J Lipid Res* 34(2): 201-210.
Traber, M. G. et al. 1998. Synthetic as compared with natural vitamin E is preferentially excreted as alpha-CEHC in human urine: Studies using deuterated alpha-tocopheryl acetates. *FEBS Lett* 437(1-2): 145-148.
Tripathi, Y. and B. M. Hedge. 1997. Effect of alpha-tocopherol pretreatment on infarct size following 90 minutes of ischemia and 4 hours of reperfusion in dogs. Indian *J Physiol Pharmacol* 41: 241-247.
Tuchweber, B. et al. 1979. Prevention by silibinin of phalloidin induced hepatotoxicity. *Toxicol Appl Pharmacol* 51: 265-275.
Wagner, H. 1999. Phytomedicine research in Germany. *Environ Health Perspect* 107(10): 779-781.
Wall, R. T. et al. 1980. Homocysteine-induced endothelial injury in vitro: A model for study of vascular injury. *Thromb Res* 18: 113-121.
Wang, M. and I. L. Goldman. 1997. Accumulation and distribution of free folic acid content in red beet (Beta vulgaris L.). *Plant Foods Hum Nutr* 50(1): 1-8.
Wang, S. Y. and W. Zheng. 2001. Effect of plant growth temperature on antioxidant capacity in strawberry. *J Agric Food Chem* 49(10): 4977-4982.
Wang, T. et al. 1985. Effects of riboflavin deficiency on metabolism of nitrosamines by rat liver microsomes. *J Natl Cancer Inst* 74(6): 1291-1297.
Watson, T. D. 1998. Diet and skin disease in dogs and cats. *J Nutr* 128(12 Suppl): 2783S-2789S.
Weisburger, J. H. 2000. Prevention of cancer and other chronic diseases worldwide based on sound mechanisms. *Biofactors* 12(1-4): 73-81.
Weretilnyk, E. A. et al. 2001. Maintaining methylation activities during salt stress. The involvement of adenosine kinase. *Plant Physiol* 125(2): 856-865.
Wichtl, M. 1994. *Herbal Drugs and Phytopharmaceuticals*. Boca Raton, FL: CRC Press. 486-489.
Williamson, E. M. 2001. Synergy and other interactions in phytomedicines. *Phytomedicine* 8(5): 401-409.
Worthington, V. 1998. Effect of agricultural methods on nutritional quality: A comparison of organic with conventional crops. *Altern Ther Health Med* 4(1): 58-69.
Worthington, V. 2001. Nutritional quality of organic versus conventional fruits, vegetables, and grains. *J Altern Complement Med* 7(2): 161-173.
Yadav, S. K. and S. Sehgal. 1997. Effect of home processing and storage on ascorbic acid and beta-carotene content of Bathua (Chenopodium album) and fenugreek (Trigonella foenum graecum) leaves. *Plant Foods Hum Nutr* 50(3): 239-247.
Yadav, S. K. and S. Sehgal. 1995. Effect of home processing on ascorbic acid and beta-carotene content of spinach (Spinacia oleracia) and amaranth (Amaranthus tricolor) leaves. *Plant Foods Hum Nutr* 47(2): 125-131.
Yang, C. M. and Y. J. Lee. 2001. Seasonal changes of chlorophyll content in field-grown rice crops and their relationships with growth. *Proc Natl Sci Counc Repub China* B 25(4): 233-238.
Yao, H. et al. 1999. An analysis of nutritional and harmful components of vegetables grown in plastic greenhouses. Zhonghua Yufang Yixue Zazhi 33(5): 304-307.
Yeom, H. W. et al. 2000. Effects of pulsed electric fields on the quality of orange juice and comparison with heat pasteurization. *J Agric Food Chem* 48(10): 4597-4605.
Yoo, J. S. et al. 1990. Effects of thiamine deficiency on hepatic cytochromes P450 and drug-metabolizing enzyme activities. *Biochem Pharmacol* 39(3): 519-525.
Young, J. F. et al. 1999. Effect of fruit juice intake on urinary quercetin excretion and biomarkers of antioxidative status. *Am J Clin Nutr* 69(1): 87-94.
Zeisel, S. H. 1992. Choline: An important nutrient in brain development, liver function and carcinogenesis. *J Am Coll Nutr* 11(5): 473-481.
Zeitlin, A. et al. 1997. The association of vitamin B12 and folate blood levels with mortality and cardiovascular morbidity incidence in the old old: The Bronx aging study. *Am J Ther* 4(7-8): 275-281.