Vitamin Research News

Dedicated to the Scientific Pursuit of Better Health

DECEMBER 2006 | Vol. 20, Number 12 | $29.95/Year U.S. ($39.95/Year International)

Table of Contents

Natural Support for Depression: New Mechanism of Action Behind Nutritional Mood Enhancers

by Chris D. Meletis, ND

Our well-being is one of the most important aspects of our health. If we do not experience the joy of living, than receiving an otherwise clean bill of health does us no good. The reality is, however, that individuals suffering from depression are also more likely to be afflicted with other diseases. One of the strongest connections made is the link that exists between depression, heart disease and diabetes. Depression occurs in up to one-quarter of patients with cardiovascular disease and diabetes.[1] In fact, depression is ranked with heart disease and diabetes as the most common chronic illnesses affecting the aging population. Depressed heart disease patients have poorer medical outcomes including increased risk of another myocardial infarction and all-cause mortality. Patients with diabetes and depression have poorer glycemic control, more diabetes symptoms, and greater all-cause mortality.[1] Clearly, depression is linked to some of the most common degenerative diseases and plays an outcome in the progression of those diseases.

Furthermore, depression is associated with actual physical symptoms that may play a role in making the cardiovascular system more vulnerable to adverse events. From a physical standpoint, depression dysregulates the hypothalamic-pituitary-adrenal axis. Depression also influences an individual's lifestyle choices and depressed patients may undertake behavior such as poor diet and exercise that may predispose them to cardiovascular disease.[1]

Continued on page 2

Inflammation Modulating Supplements

by James South, MA

[Editor's Note: This is the seventh and final article in a series paying tribute to our departed colleague James South. We are re-printing some of his most memorable articles in order to pay tribute to his vast knowledge about nutritional supplements. By continuing to share his knowledge, we are hoping to carry on his legacy.]

As I reported in the last issue of *Vitamin Research News*, chronic, often "silent" inflammation is the new plague of the 21st century.[1] This inflammation is triggered by aging and a host of lifestyle factors, including obesity/overweight, too little exercise, too much high sugar/high starch and overcooked foods, trans fatty acids, high vegetable oil intake, stress and sleep deprivation.[1]

This chronic inflammation plays a major role in a variety of diseases, including cancer, heart disease, Alzheimer's disease, diabetes, obesity, periodontal disease, allergies, asthma, depression and osteoporosis, to name just a few.[1]

In my article on inflammation I detailed a series of diet and lifestyle changes to reduce inflammation.[1] This month I report on some herbal extracts and nutrients that can effectively reduce various inflammatory mediators, including interleukin-6

Continued on page 10

Depression

Continued from front page

Studies have uncovered, however, that the simultaneous occurrence of heart disease and depression is not random but rather that depression is a risk factor for the occurrence and progression of coronary heart disease. A number of studies have investigated this link. In one study, 2,403 men and women aged 55 and over without cardiac disease were followed for just over 7 years to assess the onset of cardiac disease or cardiac death. The results indicated that subjects with major depression had an increased risk of cardiac events compared with nondepressed respondents, especially cardiac events that were of ischemic origin (angina pectoris and non-fatal myocardial infarctions).[2]

Researchers believe the link between heart disease and depression is partly due to the effect that depression has on neuroendocrine pathways, which leads to increased platelet activation as well as an excess of cortisol and catecholamines. Depression also alters autonomic nervous system function, which influences the development and progression of coronary atherosclerosis and subsequent heart disease.[3]

Another disease linked with depression is dementia. In vitro and animal studies show that inflammatory changes in the brain are pathological features of both depression and dementia and epidemiological studies show that there is a correlation between chronic depression and the likelihood of dementia in later life. This suggests that an increase in inflammation-induced cell death may play a role in the development of both of these disorders. In both depression and dementia, there is a reduction in the brain of neuroprotective components and an increase in neurodegenerative components. Such pathological changes are thought to cause neuronal damage and thereby predispose chronically depressed patients to dementia.[4]

The connection between depression and these other conditions illustrates the importance of taking steps to bolster our mental health in order to ensure our overall well being.

Serotonin—The First Piece of the Puzzle

Serotonin deficiency has long been recognized as a primary cause of depression. Serotonin promotes feelings of well being, calm, personal security, relaxation, confidence and concentration. Deficiencies of serotonin in the brain have been linked to a number of conditions, including: depression (especially the agitated, anxious, irritable type), anxiety, suicide, alcoholism, violent behavior, PMS, obesity, compulsive gambling, insomnia, carbohydrate craving, SAD (seasonal affective disorder), and migraine headaches.

Serotonin is made from the amino acid tryptophan. When neurons convert tryptophan into serotonin, they first use a vitamin B3-dependent enzyme to convert tryptophan into 5-HTP. A vitamin B6-dependent enzyme is then used to convert 5-HTP into serotonin. This process ensures that the body is nourished with proper levels of a neurotransmitter integral to mental health.

Serotonin circuits help counterbalance the tendency of two other major neurotransmitters in the brain—dopamine and noradrenaline—to encourage overarousal, fear, anger, tension, aggression, violence, obsessive-compulsive actions, overeating, anxiety and sleep disturbances. Many people suffer from various degrees of brain serotonin deficiency, leading to a host of mental, emotional and behavioral problems.

The conventional way to treat depression and serotonin deficiency is to prescribe a class of antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs). However, these drugs are associated with certain side effects, most notably an increased risk of gastrointestinal bleeding.

Natural Mood Enhancers

A number of natural substances are used to help improve mental outlook. These substances work in a variety of ways including boosting levels of serotonin, regulating circadian rhythm, preventing the atrophy of the hippocampus and reducing the inflammation that has now been linked to depression.

5-HTP

5-Hydroxytryptophan (5-HTP) is the immediate precursor in the production of serotonin from the essential amino acid L-Tryptophan. Unlike tryptophan, intestinal absorption of 5-HTP does not require the presence of a transport molecule, and is not affected by the presence of other amino acids; therefore it may be taken with meals without reducing its effectiveness. In the body 5-HTP is converted to serotonin. Whereas the pharmaceutical drugs selective serotonin reuptake inhibitors (SSRIs) affect only serotonin reuptake, not serotonin synthesis, 5-HTP effectively increases central nervous system synthesis of serotonin.[5]

5-HTP is well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. In the CNS, serotonin levels have been implicated in the regulation of sleep, depression, anxiety, aggression, appetite, sexual behavior, and pain sensation. Administration of 5-HTP has been shown to be effective in a wide variety of conditions, including depression, fibromyalgia, binge eating associated with obesity, chronic headaches, and insomnia.[6]

Melatonin

Melatonin is another mood-supporting substance. Many studies have explored how this important hormone, which is produced at night, plays a role in supporting well being.

The cyclic nature of depressive illness, the daily variations in its symptomatology and the existence of disturbed sleep-wake

Vol. 20 • Number 12 DECEMBER 2006

Vitamin Research News
Dedicated to the Scientific Pursuit of Better Health

Publisher
Robert Watson

Medical Editor
Ward Dean, MD

Editor
Kimberly Pryor

Contributors
Chris D. Meletis, ND
James South, MA
Nieske Zabriskie, ND

How to reach us: *Call 1-800-877-2447; e-mail to: mail@vrp.com; visit our website at www.vrp.com; or write to: VRP, 4610 Arrowhead Drive, Carson City, NV 89706.*

and core body temperature rhythms, all suggest that dysfunction of the circadian time keeping system may underlie the development of depression. Measurement of melatonin either in saliva or plasma, or of its main metabolite 6-sulfatoxymelatonin in urine, has documented significant alterations in melatonin secretion in depressive patients during the acute phase of illness. Not only the levels but also the timing of melatonin secretion is altered in bipolar affective disorder and in patients with seasonal affective disorder (SAD). A delay of melatonin secretion takes place in SAD, as well as changes in the onset, duration and offset of melatonin secretion.[7]

Because melatonin is so intimately tied to well-being and because it is produced primarily at night, sleep loss has been strongly associated with depression. Sleep loss, in our hectic world, has become a hallmark of modern society, leading to a reduction of melatonin levels that may explain why depression is such a common problem. In one study, healthy young males underwent 6 days of sleep restriction (a 4-hour bedtime) and 6 days of sleep recovery (a 12-hour bedtime). At the end of the sleep restriction period, researchers observed some of the same abnormalities in the subjects that are usually observed in depression. The amount of melatonin secreted in the subjects also was reduced.[8]

According to the researchers, "Since these alterations are qualitatively and quantitatively similar to those observed during aging and sometimes during depression, a state of sleep debt, as is experienced by a substantial fragment of the population in modern societies, is likely to increase the severity of depression and widespread age-related chronic conditions such as obesity, diabetes and hypertension."

St. John's Wort

St. John's wort is well known for its ability to improve well-being in patients with mild to moderate depression. In a review of the medical literature published summer 2006, researchers analyzed randomized, controlled trials of St. John's wort to determine its efficacy. All studies demonstrated a significant drop in the Hamilton Depression Rating Scale scores for clients taking St. John's wort compared with a placebo or pharmaceutical antidepressants.[9]

According to the reviewers, "Practitioners may find Saint John's wort a viable complementary treatment alternative to traditional medical treatment."

Tyrosine and Phenylalanine

The amino acids tyrosine and phenylalanine work with 5-HTP to balance brain neurotransmitters. Durk Pearson and Sandy Shaw were the first to popularize the use of phenylalanine and tyrosine to increase the synthesis of catecholamine neurotransmitters. These two stimulatory, mood-boosting amino acids are designed to be taken during the early part of the day to mimic the body's natural rhythm.

Lithium Orotate

A discussion about natural mood enhancers would not be complete without mentioning lithium orotate. Although this safe, natural form of this mineral is more commonly known for its ability to support the health of individuals with bipolar disorder, many clinicians have found it equally effective in other individuals seeking to improve mental health and well being. Dr. Ward Dean, in particular, has achieved a great deal of success using lithium in patients with standard depression.

Studies show that lithium in general inhibits the atrophy of the hippocampus. Atrophy of the human hippocampus is seen in a variety of psychiatric and neurological disorders including recurrent depression, schizophrenia, bipolar disorder, post-traumatic stress disorder, epilepsy, head injury, and Alzheimer's disease.[10]

Lithium orotate also has been found useful in subjects with alcoholism. In one study of 42 patients (33 males and 9 females), researchers treated the subjects with 150 mg per day of lithium orotate during an alcohol rehabilitation program for at least six months. The results indicated that 10 of the patients had no relapse for over three and up to 10 years, 13 patients remained without relapse for 1 to 3 years, and the remaining 12 had relapses between 6 to 12 months. The researchers noted that lithium orotate was safe and the side effects noted were minor. Eight patients developed muscle weakness, loss of appetite or mild apathy, but these symptoms subsided when the daily dose was reduced to 4 to 5 times weekly.[11]

Continued on page 4

The President's Desk

A New Day is Dawning

As the year draws to a close, I would like to thank all of you for your continued support. We are truly honored to be your partner as you pursue your healthy aging goals. Throughout 2007, we look forward to serving your health care needs and will soon introduce new features to enhance customer service.

By January, we expect to launch our new website. I'm particularly excited about this new site, which is aimed at better serving your health care needs. The new Vitamin Research Products® catalog, a valuable resource to help you design your own personal supplement regimen program, also will arrive in your mailbox next month.

Prior to the catalog's arrival, I want to prepare you for a change that we were forced to implement in order to continue to provide you with the highest quality products and service. For the first time in many years, we are adjusting prices on a number of products due to cost increases. In this newsletter's product price sheet, we are highlighting the products that will undergo a price increase beginning in January. If you'd like to know more information about price increases, feel free to contact our customer service representatives. The good news is that we have reduced prices on a small number of products and those price reductions will start this month.

With the dawning of a new year, we also will continue to keep you informed about legislative issues. With the elections over, we will continue to watch with diligence how the new party in power affects this industry. Senators Waxman and Durbin, both past opponents to the supplement industry, are now in positions of power, while Senator Orrin Hatch, a supporter of key health legislation, has now moved into a minority position. However, with new players entering the legislative picture we're hopeful there will now be more cooperation and openness in this industry. Only time will tell.

While the legislative front will always hold its uncertainties, the one thing you can count on is that VRP will partner with you in your search for optimal health—in 2007 and beyond.

Robert Watson
President/CEO

Depression

Continued from page 3

People often confuse lithium orotate with the prescription version of this mineral. However, lithium orotate is considered safer and better absorbed by the body. Dr. Dean has written extensively on lithium orotate's mechanism of action and how lithium orotate prevents the enzyme reactions responsible for the sodium depletion and dehydration effects of other lithium salts. Because of the superior bioavailability of lithium orotate, the therapeutic dosage is much less than prescription forms of lithium (150 mg/day compared to 900-1800 mg of the prescription forms.) In this dosage range of lithium orotate, there are no adverse lithium side reactions and no need for monitoring blood serum measurements.[12] Individuals who are taking other forms of lithium for depression should only discontinue them while under the supervision of a physician.

Inflammation's Emerging Role

Scientists are beginning to realize that the mechanism behind treating depression is more complex than they first thought. In fact, they are now discovering that there might be an inflammatory cause behind depression and that many of the natural mood enhancers mentioned above may work partly due to their ability to reduce inflammation. A body of evidence indicates that the therapeutic activity of natural mood enhancers is connected with their modulatory effect on the inflammatory response system.

Recently, researchers have widely investigated the link between depression and inflammation. Major depression in male patients with increased early life stress is associated with enhanced inflammatory responsiveness to psychosocial stress, providing preliminary indication of a link between major depression, early life stress and adverse health outcomes in diseases associated with inflammation.[13]

In addition, a recent study found higher levels of the inflammatory marker C-Reactive Protein (CRP) in patients with bipolar disorder compared to healthy controls.[14]

Interestingly, over the last five years, scientists have begun to explore the possible anti-inflammatory actions of St. John's wort. In a recent study, researchers decided to test St. John's wort on an animal model of acute inflammation. They injected carrageenan, an inflammatory substance, into the lung cavity of mice. This caused an acute inflammatory response characterized by fluid accumulation in the pleural cavity and a build up of various markers of inflammation. All these markers of inflammation were attenuated by St. John's wort. In addition, the carrageenan triggered increased production of nuclear factor-kappaB (NF-kappaB), an inflammatory substance, in the lung. St. John's wort significantly inhibited NF-kappaB. The researchers concluded that St. John's wort extract potently reduces the development of acute inflammation.[15]

In addition to its ability to control circadian rhythm, melatonin modulates the expression of a number of genes related to inflammation.[16] In addition, it lowers levels of the inflammatory marker NF-kappaB.[17] It may therefore have a two-pronged effect in improving mood—its ability to regulate our daily cycle and its ability to control inflammation. Because melatonin is such a potent anti-inflammatory hormone, the reason why sleep debt elicits depression-like changes may be due to the low levels of melatonin in sleep-deprived people, which triggers an inflammatory response.

Like St. John's wort and melatonin, 5-HTP is now also thought to support mental health not only through its ability to influence seratonin metabolism but also through its anti-inflammatory actions. Studies have shown that 5-HTP increases levels of Interleukin-6 (IL-6) and Interleukin-10 (IL-10). IL-6 and IL-10 are cytokines, proteins produced by white blood cells important in the body's inflammatory and immune response.[18-19] The anti-inflammatory ability of 5-HTP has led researchers to state "We speculate that the therapeutic activity of these antidepressants is at least partly connected with their effect on the cytokine network and IL-6 production."

Although lithium orotate per se has never been investigated for its anti-inflammatory actions, this would be an interesting area for researchers to explore since other forms of lithium have been shown to reduce inflammation in animal studies.[20] It is possible that one of lithium's mechanisms of actions is through a possible anti-inflammatory effect.

Conclusion

Melatonin, 5-HTP, St. John's wort, phenylalanine, tyrosine and even the mineral lithium have proved to be effective natural mood elevators. By influencing serotonin metabolism, circadian rhythm and even the health of the hippocampus, each of these substances plays a role in enhancing well being. Furthermore, scientists have recently discovered that many of these substances may work to improve mood and mental outlook through their ability to lower inflammation, indicating a surprising new mechanism of action.

References

1. Fenton WS, Stover ES. Mood disorders: cardiovascular and diabetes comorbidity. Curr Opin Psychiatry. 2006 Jul;19(4):421-7.

2. Bremmer MA, Hoogendijk WJ, Deeg DJ, Schoevers RA, Schalk BW, Beekman AT. Depression in older age is a risk factor for first ischemic cardiac events. Am J Geriatr Psychiatry. 2006 Jun;14(6):523-30.

3. Vieweg WV, Julius DA, Fernandez A, Wulsin LR, Mohanty PK, Beatty-Brooks M, Hasnain M, Pandurangi AK. Treatment of depression in patients with coronary heart disease. Am J Med. 2006 Jul;119(7):567-73.

4. Leonard BE, Myint A. Changes in the immune system in depression and dementia: causal or coincidental effects? Dialogues Clin Neurosci. 2006;8(2):163-74.

5. Turner EH, Blackwell AD. 5-Hydroxytryptophan plus SSRIs for interferon-induced depression: synergistic mechanisms for normalizing synaptic serotonin. Med Hypotheses. 2005;65(1):138-44.

6. Birdsall TC. 5-Hydroxytryptophan: a clinically-effective serotonin precursor. Altern Med Rev. 1998 Aug;3(4):271-80.

Continued on page 12

Customers' Corner Supplement Index

From pages 8-9

Product	Code
5-HTP	5767
Acetyl-L-Carnitine	4911
AGEBlock™	1985
Alpha Lipoic Acid	3455
Carnosine	4115
CeaseFire™	7072
DHEA	6371
E-Team	3111
GluControl™	1980
L-Carnitine	4821
Mito-Boost® I	1795
Mito-Boost® II	1790
Natural Libido Enhancer	1225
Oral ChelatoRx	1820
PABA	1281
Phosphatidylcholine	1241
Phosphatidylserine	3386
(R)-Lipoic Acid	3453
Resveratrol	5512
Turmeric	5102
Tryptophan	8901
UniZyme™	1630
Vitamin B12	1180

Phytonutrients and Fish Oil:
The Key to Overall Health

VRP Staff

Consuming the proper amount of fruits, vegetables and omega-3 fatty acids can be a challenge at any time of year, but never more so than around the holidays when we are faced with factors that conspire to stop us from eating healthy. The fact that at this time of year Americans are eating even less of foods that they are normally deficient in anyway is particularly disturbing due to the number of ways fruits, vegetables and omega-3 fatty acids influence our health. Studies have shown that fruit and vegetable consumption is important in immunity, heart and cognitive health and can protect against certain kind of cancers. High consumption of omega-3 fatty acids have been linked to heart health and reduced rates of depression, bipolar disorder, Alzheimer's disease and kidney cancer.

Interestingly, our genes may predetermine how many vegetables we consume on a given day. As confirmed by scientists at Rutgers University earlier this year, a genetic variation is thought to play a role in the preference for bitter-tasting vegetables. The researchers hypothesized that nontasters of a bitter substance called 6-n-propylthiouracil (PROP) would give higher ratings to bitter-tasting vegetables and would consume more bitter vegetables than would tasters of PROP. Twenty-four preschool children were identified as tasters of PROP while 41 were nontasters. Children were allowed to select from among five types of vegetables (black olives, cucumbers, carrots, red pepper, and raw broccoli) to consume in a free-choice intake test. The children were then asked to give taste ratings to the vegetables.

The results indicated that the children who could not taste PROP in the vegetables consumed more vegetables than did the children who could taste it. Only 8 percent of the PROP non-taster children consumed no vegetables in the free-choice test compared with 32 percent of taster children. The PROP non-taster children also liked raw broccoli more than did the taster children.[1] Clearly, then, finding a way to make vegetable consumption seem delicious and enjoyable is a key to increasing intake.

Even those who enjoy the taste of vegetables, however, may find that due to time constraints or other factors, consuming the recommended 7 servings of fruits and vegetables per day is difficult. A September 2006 study in the *Journal of the American Dietetic Association* found that only 40 percent of Americans eat an average of five or more 1/2-cup servings of fruits and vegetables per day. The article concluded that Americans need to consume more fruits and vegetables, especially dark green and orange vegetables and legumes. The authors also noted that the new recommendations for fruit and vegetable intakes are greater than the familiar five servings a day proclaimed in the past.[2]

Another grim statistic was offered up in a recent study of 180 children. Up to 36 percent of boys and 24 percent of girls reported not eating any fruit or vegetables on the recording day.[3] With fish oil, the outlook isn't much better. A recent study found that most Americans need to increase their omega-3 intake by 3.5 grams per day in order to give them the same low rates of heart disease and depression found in high-seafood-consuming Japan.[4]

Costly to Our Health

One study estimated that 892,000 lives in the old European Union countries and 423,000 lives in the 10 new European Union countries would potentially be saved if fruit and vegetable intake increased to 600 grams per person per day. The researchers further estimated that in those countries ischemic heart disease and stroke could be reduced by up to 24 percent and 15 percent respectively with increased fruit and vegetable consumption and that potential reductions for selected cancers ranged from 1 percent to 17 percent.[5]

Other studies have shown that the greater the consumption of fruit and vegetables, the lower the risk of coronary heart disease.[6] A recent review of the medical literature also showed that consuming the omega-3 fatty acids EPA plus DHA at less than one gram per day protects against heart attacks, mostly due to suppression of fatal arrhythmias rather than stabilization of atherosclerotic plaques. At doses greater than 3 grams per day, the review found, EPA plus DHA can improve cardiovascular disease risk factors, including decreasing plasma triglycerides, blood pressure, platelet aggregation, and inflammation, while improving vascular reactivity.[7]

Because there is increased heart attack incidence immediately after the holidays lasting into late winter, phytonutrient and omega-3 consumption at this time of year could play an important role in heart health in the months to come.

Conclusion

Consuming enough fruits, vegetables and omega-3 fatty acids through the diet alone is likely an impossible challenge for most individuals, especially during the holidays. Consequently, finding pleasant-tasting ways to supplement dietary intake, by consuming an organic green drink such as Primary Greens and Nordic Naturals fruit-flavored fish oil supplements, can help maintain overall health.

References

1. Bell KI, Tepper BJ. Short-term vegetable intake by young children classified by 6-n-propylthoiuracil bitter-taste phenotype. Am J Clin Nutr. 2006 Jul;84(1):245-51.

2. Guenther PM, Dodd KW, Reedy J, Krebs-Smith SM. Most Americans eat much less than recommended amounts of fruits and vegetables. J Am Diet Assoc. 2006 Sep;106(9):1371-9.

3. Cade JE, Frear L, Greenwood DC. Assessment of diet in young children with an emphasis on fruit and vegetable intake: using CADET--Child and Diet Evaluation Tool. Public Health Nutr. 2006 Jun;9(4):501-8.

4. Hibbeln JR, Nieminen LR, Blasbalg TL, Riggs JA, Lands WE. Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. Am J Clin Nutr. 2006 Jun;83(6 Suppl):1483S-1493S.

5. Pomerleau J, Lock K, McKee M. The burden of cardiovascular disease and cancer attributable to low fruit and vegetable intake in the European Union: differences between old and new Member States. Public Health Nutr. 2006 Aug;9(5):575-83.

6. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. J Nutr. 2006 Oct;136(10):2588-93.

7. Breslow JL. n-3 fatty acids and cardiovascular disease. Am J Clin Nutr. 2006 Jun;83(6 Suppl):1477S-1482S.

AGEs and Cross-Linkages:
Their Role in Weight Gain, Heart Health, and a Surprising Number of Conditions

by Nieske Zabriskie, ND

Research has shown that intake of sugar, carbohydrates, and high-glycemic-index foods is increasing in the United States. From 1970 to 1996, the intake of added sugars in the diet primarily in the form of soft drinks, snacks, desserts and sweetened juice rose by 23 percent.[1] More recent studies on sugar intake with adolescents suggest that this trend is continuing.[2] This increase in sugar and carbohydrate consumption is alarming given that diets high in sugar have been implicated to cause or exacerbate numerous diseases. Some of these include diabetes, obesity, elevated lipids, and cardiovascular disease.

Elevated blood sugar has been shown to cause several physiological reactions in the body leading to disease. One of these reactions, known as glycosylation, involves adding sugars to molecules. When reduced sugars are attached onto biological proteins "Advanced Glycosylation End products" (AGEs) are formed in a process known as the Maillard reaction. This reaction, which occurs when foods are browned, is irreversible, causing these proteins with sugars attached to accumulate over time. One well-known example of AGEs is hemoglobin A1C, which is frequently measured to evaluate long-term blood sugar control in diabetics.

It is proposed that AGE formation is a normal physiological process that functions as a signal for recognition of old molecules to be broken down and excreted by the kidneys. With increasing age, however, the excretion of these molecules decreases.

AGE formation and accumulation is greatly accelerated with high levels of circulating sugars and oxidative stress seen in conditions such as diabetes. A study was performed with individuals diagnosed with type 1 diabetes. The investigation demonstrated a significant increase in AGE levels and pro-inflammatory markers with increased variability of blood sugar levels after eating.[3] AGEs are ingested in the diet generally in the form of foods undergoing prolonged heating, particularly fats, meat and meat-substitutes, and broiled foods. In individuals with normal kidney function, only about one-third of ingested AGEs are excreted in the urine within 48 hours and less AGE excretion is found with kidney disease. Also, serum AGE cross-linking is significantly increased after ingestion of an AGE-containing meal.[4] Animal studies also indicate that high-fat diets are correlated with obesity, tissue damage, and increased levels of AGEs.[5] AGEs can be inhaled through tobacco smoke as well.[6]

Physiological reactions involving AGEs have been implicated in the pathology of numerous diseases. AGEs react with molecules creating cross-linkages. Proteins and other large molecules such as lipids can undergo cross-linking reactions that cause them to become less elastic and less digestible by enzymes for degradation. Conditions such as diabetes with elevated blood sugar, known as hyperglycemia, show an increase in glycosylation of proteins, which may be the causative link with the increase in chronic diseases seen in individuals with diabetes. AGEs have been implicated in the vascular changes found with diseases of the nerves, kidneys and eyes in diabetic individuals.[7]

AGEs and Cardiovascular Disease

AGE accumulation is associated with cardiovascular dysfunction and disease such as atherosclerotic plaque formation, decrease in vascular and cardiac elasticity, endothelial dysfunction, and hypertension.[8] More specifically, AGEs have been shown to quench nitric oxide (NO), which is an endothelium-derived relaxing factor in smooth muscle. Quenching NO impairs this relaxation and is associated with the pathology seen with hypertension, atherosclerosis, and diabetes. AGEs also interact with specific cell receptors known as RAGE. AGEs lead to chronic activation of RAGE. This is damaging to the body because studies indicate that RAGE activation may lead to an increase in inflammatory markers and cellular injury.[9]

AGEs and Metabolic Syndrome

Metabolic syndrome is a medical condition characterized by central obesity, elevated triglycerides, small low-density lipoprotein (LDL) particles, low beneficial high-density lipoprotein (HDL) cholesterol, elevated blood pressure, increased inflammation, and insulin resistance. AGE accumulation and RAGE expression is correlated with the symptoms of this condition. A variant of RAGE known as endogenous secretory RAGE (esRAGE) is believed to be a decoy receptor for AGEs and increased levels of esRAGE have been shown to be protective in atherosclerosis and metabolic syndrome. Additionally, esRAGE levels are inversely correlated with body mass index, blood pressure, insulin resistance, and triglycerides.[10]

AGEs and Other Common Diseases

Additionally, cross-linkage of collagen caused by increased levels of AGEs impairs cartilage repair mechanisms and is associated with increased severity of osteoarthritis.[11] Research also indicates that toxic AGEs are found in the brain in individuals with Alzheimer's disease[12] and also have been linked to cataracts[13] and rheumatoid conditions such as arthritis and fibromyalgia.[14] Women with polycystic ovary syndrome have increased levels of AGEs and RAGE expression without evident elevated blood sugar possibly explaining the increased cardiovascular risk seen in these women.[15] RAGE activation is also implicated in the invasion and spread of several types of cancer cells.[16]

Prevention of AGE Formation

Preventing AGE formation and the resultant cross-linking may be the key to

prevention of numerous age-related diseases. A number of natural substances have been studied showing benefit in this area.

Carnosine

Carnosine is a dipeptide consisting of beta-alanine and L-histidine. It is found only in animal tissues and particularly in high concentrations in skeletal muscle, cardiac muscle, and the brain. Research shows that carnosine can prevent the formation of AGEs, cross-linking, glycation, and protein carbonyl group formation.[17] Studies indicate that muscle carnosine levels decrease significantly with age demonstrating a 63 percent decrease from age 10 to age 70.[18] Carnosine acts as an antioxidant decreasing lipid oxidation, protecting membranes from free radical damage, regulating white blood cell function, and chelating reactive metals. In fact, carnosine has been shown to scavenge metabolites from lipid peroxidation preventing DNA-protein and protein-protein cross-linking reactions. Interestingly, it is the high carnosine concentrations in animal tissue that led one group of researchers to suggest that carnivorous diets may be protective for complications associated with high blood sugar and aging.[17]

Preliminary, in vitro studies also indicate that carnosine may have a role to play in stopping AGE-induced cell proliferation and death. Specifically, AGEs were added to skin cell cultures and incubated. Increased cell death was seen beginning at the 7th day and continued for up to 10 days. Antibodies to AGE cell receptors were used with similar results. Free radical scavengers such as L-carnosine, when added to the cell cultures, decreased AGE-induced cell death.[19]

Galega officinalis

Galega officinalis, also known as Goat's rue or French lilac, is a plant traditionally used to support blood sugar health. The active ingredient found to lower blood glucose is galegine or isoamylene guanidine. Goat's rue has been found to lower blood sugar in both normal and diabetic humans.[20] It also has demonstrated antiplatelet aggregation and antibacterial activity.

Pyridoxine

Pyridoxine, or vitamin B6, is converted to several active metabolites such as pyridoxamine and pyridoxal-5-phosphate. Vitamin B6 is a required cofactor in enzymatic reactions involved with amino acid, lipid, and carbohydrate metabolism. Pyridoxamine has been shown to decrease AGE formation by reacting with carbonyl intermediates in the Maillard reaction. Pyridoxamine also exhibits free radical scavenging activity by scavenging toxic products of sugar and lipid degradation and inhibiting reactive oxygen species. Additionally, studies indicate that pyridoxal and pyridoxal phosphate significantly inhibited glycosylation of the protein albumin.[21] Research has demonstrated that glucose consumption is correlated with decreased pyridoxal-5-phosphate and total plasma vitamin B6 levels.[22]

Thiamine

Thiamine, or vitamin B1, is a required cofactor in carbohydrate metabolism and is associated with reduced AGE accumulation. Research indicates that thiamine pyrophosphate is a potent inhibitor of AGE formation.[23] The lipid-soluble derivative of thiamine, benfotiamine, has also been shown to inhibit AGE formation and pro-inflammatory mediators as well decrease diabetic complications such as retinal disease.[24] Studies with individuals with hyperglycemia demonstrate that thiamine supplementation improves the relaxation of the smooth muscle around blood vessels known as endothelium-dependent vasodilation, which may potentially decrease the risk of cardiovascular complications.[25]

Xylitol

Xylitol is a naturally occurring 5-carbon sugar alcohol found in most plant material and made by the body during normal metabolic processes. Xylitol is used as a dietary sugar substitute and has Generally Recognized as Safe (GRAS) status in the US. A study with diabetic patients showed that using xylitol as a dietary sweetener caused less of a rise in the levels of blood glucose than using sucrose.[26] Although no direct studies exist correlating the use of xylitol as a sugar substitute with decreased AGE production, the fact that it causes a lower rise in blood sugar after a meal in at-risk patients implies there may be a potential positive association between low-glycemic sugars such as xylitol and decreased AGE formation.

Some researchers believe that diets high in sucrose and fructose increase AGE production. One study compared the ability of fructose and glucose to induce cross-linking reactions with the protein albumin. The researches demonstrated that fructose induced cross-linking 10 times faster than glucose suggesting fructose may be important in cross-linking reactions in vivo.[27] Additional studies show that long term consumption of fructose increased AGEs. In fact, one study demonstrated that fructose-fed rats had significantly higher blood fructose levels, cholesterol, and levels of the AGE glycosylated hemoglobin compared to rats fed other sugars and control rats.[28] Additionally, an animal study showed that obesity directly impacts oxidative stress and AGE formation and that weight loss in obese animals improved levels of AGEs.[29] Therefore, using xylitol as a low-calorie sweetener to enhance weight loss and replace other high-glycemic, AGE-producing sweeteners can be an important part of an AGE-prevention strategy.

Conclusion

Natural strategies have proved successful in decreasing the accumulation and detrimental effects of AGEs. As Americans increase their dietary sugar intake, interventions such as these may provide significant disease risk reduction in diabetes and secondary complications, cardiovascular disease, and many other age-related conditions.

References

1. Johnson RK, Frary C. Choose beverages and foods to moderate your intake of sugars: the 2000 dietary guidelines for Americans--what's all the fuss about? J Nutr. 2001 Oct;131(10):2766S-2771S.

2. Striegel-Moore RH, Thompson D, Affenito SG, Franko DL, Obarzanek E, Barton BA, Schreiber GB, Daniels SR, Schmidt M, Crawford PB. Correlates of beverage intake in adolescent girls: the National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr. 2006 Feb;148(2):183-7.

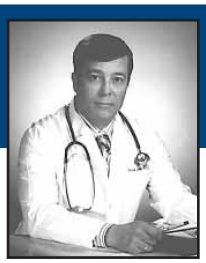
3. Ahmed N, Babaei-Jadidi R, Howell SK, Thornalley PJ, Beisswenger PJ. Glycated and oxidized protein degradation products are indicators of fasting and postprandial hyperglycemia in diabetes. Diabetes Care. 2005 Oct;28(10):2465-71.

4. Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci U S A. 1997 Jun 10;94(12):6474-9.

5. Li SY, Liu Y, Sigmon VK, McCort A, Ren J. High-fat diet enhances visceral advanced glycation end products, nuclear O-Glc-Nac modification, p38 mitogen-activated protein kinase activation and apoptosis. Diabetes Obes Metab. 2005 Jul;7(4):448-54.

6. Cerami C, Founds H, Nicholl I, Mitsuhashi T, Giordano D, Vanpatten S, Lee A, Al-Abed Y, Vlassara H, Bucala R, Cerami A. Tobacco smoke is a source of toxic reactive

Continued on page 13



CUSTOMERS' CORNER

by **Ward Dean, MD**
Medical Director

Lou Gehrig's Disease

Dear Dr. Dean,

I'm a corporate wellness coach for a large oil company. We have an employee who has a wife with Amyotrophic Lateral Sclerosis (ALS – Lou Gehrig's disease). She will probably only live about one to two more years at her progression rate. They are looking for something to assist her with her hypertonic muscle stiffness and low morning energy. I have recommended some liquid nutrition we used in endurance racing, as she cannot normally chew regular food anymore with her fading gag reflex. They are not asking for a cure or magic bullet—but are wondering if there was anything that might help her be just a little bit more comfortable. Does such a supplement exist or do you have any suggestions? I hope you are well!

In health,
Mr. J.

Dear Mr. J.,

The single nutrient that has been documented to help ALS is *L-Carnitine*. *Acetyl L-Carnitine* (*ALC*) may be even better. ALS may be mitochondrial-related. Consequently, I think *Mito-Boost® I* and *II* may be helpful. I'd probably add a little extra *L-Carnitine* or *ALC*.

In addition, I'd consider *Phosphatidylcholine* and *Phosphatidylserine*. Sublingual *Vitamin B12* (or weekly B12 injections, if her physician will prescribe them) may help with her energy.

Finally, if her physician will co-operate (and this is a big "if") I'd try low-dose GHB (Xyrem®) by prescription—maybe 250-500 mg or so every 3-4 hours. Low-dose GHB is a great mood-enhancer, muscle relaxant and energizer, all at the same time. Higher doses, of course, result in euphoria and natural sleep. GHB works beautifully for many conditions, and may even help ALS.

Obviously, a lot of the above is "educated guess work"—but none of the recommendations will hurt. The hardest part will be getting someone with ALS to take that much stuff. *Mito-Boost I*, being a drink mix, may be the easiest, most effective, and best starter. Sublingual *B12* or shots, next. Xyrem does not taste great (very salty), but is also a liquid, so it should not be a problem.

Let me know how she does.

Ward Dean, M.D.

Depression & *5-HTP*

Dear Dr. Dean,

First I want to say you have many great products and I have been noticing an improvement in my health and well being since I found your website and started using some of your products.

My question is regarding my mother. She is currently taking the antidepressant Effexor XR® 75 mg, 1 per day. I have advised her that *5-HTP* may be a good alternative to try instead of Effexor since she has been experiencing some of the milder side effects of the drug. I advised her to ask her doctor how to wean off the Effexor in order to start on the *5-HTP* but I wanted your opinion on this as well. Also she is concerned that while trying to switch between the two, her symptoms will return. Is this a legitimate concern? Could she try small doses of the *5-HTP* as she is weaning off the Effexor?

Thank you.
Mr. P.

Dear Mr. P.,

Your mom can begin taking *5-HTP* while still on Effexor. In fact, that is what I recommend for most people. Over a period of weeks, she can try reducing her dosage of Effexor.

I recommend starting with 33 mg of *5-HTP* (on an empty stomach) about 3 times per day, plus 50-100 mg about an hour before bedtime. She should, of course, discuss changing her Effexor dosage with her physician.

Hope this answers your question.

Ward Dean, M.D.

Anxiety Attacks

Dear Dr. Dean,

My mother, who has been your customer for years, is 80 years old. She is taking Armour® for thyroid, Boniva® for osteoporosis, and a blood pressure medication. In the last year, she has been experiencing anxiety attacks—mostly at night. She wakes up with her heart beating and feeling a terrible fear to the point that she cannot stay in bed. When you ask her what she is afraid of, she doesn't have anything specific. She is just afraid of what the day might bring. She is getting very little sleep. She also is on all natural hormones prescribed by her alternative doctor; so I know the levels of her hormones are correct. She does saliva tests at least once each year. She just had her six-month physical and everything was fine there. I don't want to start her on something like Zoloft®. I'm not sure that would make her sleep anyway. What would you recommend?

Ms. T.

Dear Ms. T.,

First, when does she take her thyroid medication? In the morning, or at night? Some people, especially the elderly, are exquisitely sensitive to slight variations in their thyroid hormone dosage. If she is taking the thyroid at night, that may be the cause of her palpitations. Adjustment of her dosage or the timing of taking her thyroid may solve the problem.

Second, what medication is she taking for her blood pressure? If she is not on a beta blocker already (i.e. inderal, metoprolol, atenolol, etc.) I'd consider asking her physician to consider changing her medication to a beta blocker. Beta blockers block the "fight or flight" reaction, preventing anxiety-related palpitations, sweaty palms, rapid heart rate, etc.

To promote natural sleep, I recommend 100-200 mg of *5-HTP* or 1,000-2,000 grams of *L-Tryptophan* about an hour before bedtime on an empty stomach.

Ward Dean, M.D.

Peyronie's Disease

Dear Dr. Dean,

I am a 57-year-old male with erectile dysfunction and Peyronie's disease. The ED started about three years ago and I developed PD around one year later. Five years ago I had colon cancer, which thankfully was diagnosed early and I had a quick recovery. I have been checking the Internet and I have read a number of articles indicating *DHEA* might help. The ED came on very quickly if that is any help. I believe I developed the PD through the injections given to me by a local men's health clinic.

Regards,
Mr. H.

Dear Mr. H.,

I think *DHEA* is very important for many reasons, but don't expect miracles from it for what you've got. I usually recommend testosterone cypionate, 200 mg injections every 2-3 weeks, and Arimidex® (1/2-1 mg twice per week, to block conversion of testosterone to estrogen). Also, since you've got to get both of these from your physician, I recommend a prescription for Cialis® or Levitra® as well.

A nutritional alternative to Cialis/Levitra is a daily combination of several grams each of *L-Arginine* and *Choline*, and 500-1,000 mg of *Pantothenic Acid* (Vitamin B5).

If your physician refuses to prescribe Arimidex, but does prescribe testosterone, add *Resveratrol*, 20-40 mg per day to your regimen, as an anti-estrogen substance. If your physician won't prescribe testosterone, I recommend *Tribulus Terrestris*, *Pantothenic Acid*, *L-Arginine*, and *Choline*, which are all found in *Natural Libido Enhancer*.

With regard to Peyronie's disease, the injections you received may or may not have been related to it. I think Peyronie's is much more common than the statistics reflect. I think a lot of cases go unreported. There are many reported (but unconfirmed) causes—and likewise many proposed treatments—none of which, unfortunately, are predictably effective. Many cases of Peyronie's resolve spontaneously after months or years, for no apparent reason. Among the proposed and tested treatments are *Vitamin E* (400-800 IU QD) and *Para-amino benzoic Acid* (PABA) up to 12 grams per day—the limiting factor is usually nausea. I recommend starting with 1-2 grams of *PABA* per day, increasing the dose gradually based on gastrointestinal tolerance. It should be noted that this is an "FDA-approved" indication for *PABA*. Other options include *Acetyl-L-Carnitine* (*ALC*) 1-3 grams per day, *Carnosine* 1-2 grams per day, and EDTA (as in *Oral ChelatoRx*).

All of the above recommendations are based on the pathogenesis of Peyronie's disease, i.e., increased fibrosis/cross-linking of collagen in the penis. These recommendations, alone or in combination, have powerful anti-cross-linking properties. In this regard, I'd also add the premier anti-cross-linking formula, *AGEBlock*™.

Ward Dean, M.D.

Blood Thinners

Dear Dr. Dean,

Is there a substitute for Warfarin blood thinner, and what do you suggest?

Mr. V.

Dear Mr. V.,

I rarely, if ever, use prescription "blood thinners." Instead, I use a combination of *Oral ChelatoRx*, *Turmeric* extract (2-3 grams per day), *UniZyme*™ (2 caps, 3 times per day), *Resveratrol* (20-40 mg per day), and a daily baby aspirin. All of these are not required in every case.

Ward Dean, M.D.

Blood Sugar Control

Dear Dr. Dean,

I have switched from *Alpha-Lipoic* to *R-Lipoic Acid* and question if this will still meet my requirement for blood sugar control. Or shall I take both?

Your very satisfied customer,
Mr. D.

Dear Mr. D.,

I've found that *R-Lipoic Acid* is about twice as potent as *Alpha-Lipoic Acid*. Therefore, you can probably accomplish your goal with half as much *R-Lipoic* as you were taking of *Alpha-Lipoic*.

Also, if you are not doing so already, consider taking *GluControl*™ a premiere blood-sugar supporting supplement.

Ward Dean, M.D.

Acne Vulgaris

Dear Dr. Dean,

In your May 2006 newsletter, the article titled Skin Health had suggested a link between H. pylori and the occurrence of acne rosacea. This article was read with great interest because all of my children have suffered from acne vulgaris, which as you know causes frequent, large, unsightly pimples on the face, shoulders, chest and back with resultant scarring and pitting of the skin. A recent trip to the dermatologist proved to be fruitless. Since my children were allergic to benzyl peroxide, most topical acne medications could not be used. I refused to follow the dermatologist's suggestion of placing them on long-term, low-dose antibiotics due to the adverse effects of such a protocol.

After reading the newsletter article, I immediately placed all of my children on *CeaseFire*™. After two weeks of taking *CeaseFire*, the acne had dramatically improved. An occasional pustule still forms, but they are much smaller than before. I am amazed at how quickly their condition responded to such a simple treatment. I am happy to say that my teenagers are no longer embarrassed by unsightly acne. Even though the article did not discuss the use of *CeaseFire* for this particular form of acne, I wanted to share my family's success with you and your readers. Perhaps others may find relief from this embarrassing and disfiguring skin condition.

Sincerely,
Mrs. H.

Dear Mrs. H.,

I'm glad you had such wonderful success with *CeaseFire*™. We receive so much positive feedback about our suggestions but acne is such a burden for young adults I felt your letter needed to receive special attention. Consequently, we are publishing it. Thanks for sharing your story.

Ward Dean, M.D.

Be sure to visit the dear doctor section at www.vrppet.com where you'll find questions and answers like these about your pets. You can also ask questions at dearvet@vrppet.com

Inflammation

Continued from front page

(IL-6), IL-1 beta, TNF-alpha, prostaglandin E2 and leukotrienes.

Stephania tetrandra

Stephania tetrandra is an herb used in China and Korea to treat various inflammatory conditions, including rheumatoid arthritis, lung silicosis and hypertension.[2,3] Its main anti-inflammatory components have been found to be tetrandrine (Tet) and fangchinoline (Fang).[4] Stephania extracts concentrate these two ingredients so that their combined level represents 10 to 20 percent of the extract. A Stephania preparation has shown significant effect in reducing the neutrophil-induced inflammation in rheumatoid arthritis.[5]

Tet and Fang have been shown to suppress multiple inflammatory cytokines and mediators. Tet powerfully suppressed nuclear factor kappa Beta (NFkB) activation in human T cells (immune cells).[6]

NFkB is a multimodal inflammation factor that promotes production of powerful inflammatory cytokines including IL-1, IL-6, IL-8 and tumor necrosis factor-alpha.[7] Tet effectively reduced conjunctivitis in mice exposed to ragweed pollen, reducing inflammatory cytokines IL-1 beta and IL-5, while also reducing mast cell degranulation (source of histamine).[8]

All of these are part of the cause of allergen-triggered red, itchy, irritated eyes. Tet and Fang powerfully suppressed formation of thromboxane B2 by human platelets, reducing their tendency to form unnecessary clots.[9] Tet and Fang reduced by 90 percent the production of IL-1 and tumor necrosis factor-alpha when human monocytes (white blood cells) were activated by germs.[10]

Tet showed potent inhibitory effect on leukotriene and prostaglandin (PG) generation by human monocytes and neutrophils.[11] Tet did not directly inhibit the cyclooxygenase (COX) enzyme that makes inflammatory PGs, but rather acted like a corticosteroid to inhibit arachidonic acid release from cell membranes, thereby depriving the COX enzyme of the raw material needed to make PGs.[11]

Perhaps most importantly, both Tet and Fang have shown powerful (63 to 86 percent) suppression of IL-6 activity, even at very low concentrations. IL-6 becomes especially problematic with aging, obesity, stress and sleep deprivation.[1] IL-6 is the main cause of elevated blood C-reactive protein, a major risk factor for heart disease.[1]

5-Loxin®

5-Loxin® is a special extract of boswellic acids from the traditional East Indian herb frankincense (*Boswellia serrata*). 5-Loxin contains approximately 30 percent AKBA (acetyl-II-keto-beta-boswellic acid), due to a patented process that converts other beta-boswellic acids to AKBA. AKBA is a selective inhibitor of 5-lipoxygenase (5-Lox).[12]

5-Lox converts arachidonic acid (made within the body from linoleic acid in vegetable oils) to the highly inflammatory leukotrienes.[13] Leukotrienes promote cancer,[14] damage the brain,[13] and promote asthma, arthritis, psoriasis and colitis.[14] They may also promote atherosclerosis.[15] 5-Lox is activated by stress-released cortisol.[16] Boswellia extracts have been used successfully to treat ulcerative colitis,[17] asthma,[18] ileitis[19] and osteoarthritis.[20]

Traditional Boswellia extracts typically contain 2 percent or less AKBA.[20] Other boswellic acids show little or no 5-Lox inhibition, and some may even counteract AKBA's inhibition of 5-Lox.[12] Thus 5-Loxin represents a superior form of Boswellia extract, which works at much lower potencies than traditional Boswellia extracts.

Luteolin

Luteolin is a flavone (flavonoid) widespread in nature, present in foods such as celery, green pepper, perilla leaf and seed and chamomile.[21] According to Kotanidou and colleagues, "Luteolin is…among the most potent and efficacious flavonoid inhibitors of LPS [germ cell wall fragment]-induced TNF-[alpha], interleukin-6 production and inducible nitric oxide expression."[21]

Luteolin possesses strong anti-inflammatory and anti-allergic activity in vivo (living organism).[22] In mice given LPS to induce sepsis, luteolin increased the survival rate from 4 percent (untreated) to 48 percent (luteolin-treated).[21]

When compared to other flavonoids, such as quercetin, myricetin, chrysin, apigenin and taxifolin, only luteolin successfully inhibited TNF-alpha production and reduced several forms of inflammatory edema when given orally to test animals.[23]

Luteolin inhibited mast cell release of histamine in rats challenged with IgE (allergy) antibodies.[24] In studies with human colon cells, luteolin effectively suppressed TNF-alpha and IL-8 production.[25] Luteolin also inhibited the release of histamine, leukotrienes and PGD2 from cultured human mast cells sensitized with IgE antibody.[25]

Unlike many flavonoids, luteolin has been shown to be well-absorbed orally by animals and humans, and to be highly bioavailable (taken up by body cells).[21-23,27-28] Luteolin has been shown effective even at low levels.[21-23] Luteolin, along with Stephania, may be one of the most broad-spectrum anti-inflammatory "nutrients."

Stinging Nettle Leaf

Stinging Nettle (*Urtica dioica*) is an herb that grows throughout the temperate zones of Europe and America. It has been used as a medicine since ancient times and has been used to treat inflammatory conditions such as asthma, eczema and rheumatic conditions. In Germany a nettle leaf extract is approved as adjuvant therapy of rheumatic diseases (joint or musculoskeletal inflammatory conditions).[29]

Nettle leaf extract (NLE) has been shown to reduce IL-2 and interferon-gamma release by monocytes, which "may inhibit the inflammatory cascade in autoimmune diseases like rheumatoid arthritis."[29] NLE was shown to reduce secretion of TNF-alpha by human dendritic cells, leading to reduced T cell-mediated inflammatory response.[30] Mice suffering colitis treated with NLE exhibited fewer signs of colitis than untreated mice. The treated mice also had significantly lower levels of IL-1 beta and TNF-alpha than untreated mice.

Monocyte proliferation (which promotes inflammation) after LPS stimulation was also less in treated mice.[31] When 20 healthy humans ingested NLE for 21 days, there was an 80 percent reduction in TNF-alpha and a 99 percent reduction in IL-1 beta when blood samples were stimulated with LPS ex vivo (outside the body).[32] NLE has also been shown to inhibit NFkB activation.[33] NLE thus exhibits multimodal anti-inflammatory activity.

Holy Basil

Holy basil (*Ocimum sanctum*) is an East Indian herb highly esteemed in Ayurvedic medicine.[34] Newmark and Schulick report holy basil leaf extract (HBE) to be an inhibitor of both cyclooxygenase-2 (COX-2) and 5-lipoxygenase.[34] Kelm and colleagues found various compounds in holy basil leaves to be effective COX-2 inhibitors.[35] A key constituent of HBE is ursolic acid.[34] Ringbom and associates reported ursolic acid to be an effective COX-2 inhibitor.[36]

Godhwani and coworkers tested HBE in rats and found that it was about 60 percent as effective as sodium salicylate (an aspirin-related compound) in reducing inflammation in various tests.[37] HBE has also been shown to reduce corticosterone release in response to noise stress in rats.[38,39]

This is a novel anti-inflammatory property of HBE, given that noise stress is ubiquitous in the modern world, that noise stress can increase cortisol release in humans, and that cortisol activates 5-lipoxygenase, producing inflammatory leukotrienes.[16] As a COX-2 inhibitor (not as powerful, and thus safer, than the prescription COX-2 inhibitors that have made recent headlines), HBE represents an important herbal anti-inflammatory agent.

Green Tea Polyphenols

Dona and colleagues stated, "Green tea is rich in flavonoids and indeed epidemiological, in vitro, and animal-model studies have associated green tea consumption with health benefits, including decreased inflammation."[40] The researchers found both EGCG (the most important green tea polyphenol) and green tea extract (GTE) inhibited neutrophil-mediated angiogenesis in an in vivo inflammatory angiogenesis model.[40]

Inflammation-induced angiogenesis (growing new blood vessels) helps tumors create the massive blood supply they need for growth. Researchers also found that oral GTE enhanced resolution in a mouse lung inflammation model, significantly reducing subsequent fibrosis.[40]

Ahmed and associates found EGCG reduced expression and activity of COX-2 in human chondrocytes (cartilage-producing cells) from osteoarthritis cartilage.[41] They also found GTE reduced inflammatory PGE2 production when the chondrocytes were stimulated with IL-1 beta.[41]

Kundu and coworkers found that mice pretreated with oral GTE had reduced COX-2 expression when stimulated by a tumor promoter.[42] Wheeler and associates found that EGCG inhibited NFkB activation in human lung epithelial cells treated with IL-1 beta, which is a powerful activator of NFkB.[43] The same researchers had also previously shown that EGCG inhibits TNF-alpha activation of super inflammatory NFkB.[43]

Aktas and colleagues found that EGCG reduced the severity of experimental autoimmune encephalomyelitis (inflammatory brain disease) when mice were orally pretreated with EGCG.[44] They also found that EGCG significantly reduced TNF-alpha production in the mice.[44]

Hussain and coworkers found that EGCG inhibited COX-2 without inhibiting COX-1 expression (COX-1 is important for intestinal and kidney health) in several different types of human prostate cancer cells.[45]

Varilek and associates found that GTE attenuated chronic inflammation in mice suffering inflammatory bowel disease, demonstrating lower interferon-gamma and TNF-alpha levels than control mice with colitis that were not given EGCG.[46] Thus EGCG-rich green tea extract also qualifies as a broad-spectrum anti-inflammatory agent.

Ginger Root

Ginger (*Zingiber officinalis*) has been used throughout the world for thousands of years as a medicine. It is called the "universal medicine" in East Indian Ayurvedic medicine. Ginger root contains a veritable cornucopia of natural anti-inflammatory compounds.[47] The USDA Phytochemical Database reported as of 1999 that ginger has more 5-lipoxygenase inhibitors than any other botanical source.[47]

Dr. Srivastava reported excellent results with ginger root in 56 patients with various rheumatic complaints, with over 75 percent getting relief in pain and swelling. He suggested that ginger inhibits both inflammatory prostaglandin (COX-2) synthesis and leukotriene (5-lipoxygenase) synthesis.[48]

Newmark and Schulick note: "Ginger has multiple constituents that inhibit COX-2 and inhibit the 5-lipoxygenase metabolism of arachidonic acid…Ginger inhibits the creation of prostaglandin PGE2, which [gives ginger] strong antipyretic (or anti-heat) producing effects. It balances production of inflammatory prostaglandins [PGE2] and PGI2, which also regulates the production of compounds that dilate the arteries. Ginger's constituents safely restore healthy platelet function by inhibiting the formation of…thromboxanes.... Ginger reduces prostaglandins that sensitize pain receptors at nerve endings…; [and] has significant anti-ulcer effects [which shows that ginger does not suppress intestine-essential COX-1 while suppressing COX-2]…."[47] Jalad and colleagues reported that "Most of the [ginger root] fractions containing gingerols and/or gingerol derivatives showed excellent inhibition of LPS-induced PGE2 production."[49] Park and associates found that topical gingerol "suppressed TPA-induced…[skin] inflammation" in mice.[50]

Given its balanced anti-COX-2 and anti-5-lipoxygenase activity, ginger root extract provides useful, yet safe anti-inflammatory activity.

Inflammation Control

To help support those who struggle with long-term chronic inflammation, we have developed two products, Inflammation Control and Advanced Inflammation Control.

Advanced Inflammation Control is a four-capsule-daily formula, containing Stephania tetrandra extract; 5-Loxin, luteolin, stinging nettle leaf extract, green tea extract and ginger extract. It is a synergistic, state-of-the-art, inflammation-modulating formula.

For those desiring a more basic formula, we also offer Inflammation Control, a combination of Stephania and luteolin.

Chronic silent inflammation is probably the most insidious yet pervasive health problem in America today. Now, well-researched, high-tech herbal nutrition can be used to douse the hidden fires of inflammation.

References

1. South J. America's Inflammation Epidemic. The new "plague" of our times. Vit Res News. November 2006;20(11).

2. Choi H, et al. Anti-inflammatory effects of fangchinoline and tetrandrine. J Ethnopharmacol. 2000;69:173-79.

3. Ho L, et al. Plant alkaloid tetrandrine downregulates Ikappa B alpha kinases-Ikappa Balpha-NF-kappaB signaling pathway in human peripheral blood T cell. Br J Pharmacol. 2004;143:919-27.

Continued on page 12

Inflammation

Continued from page 11

4. Shen Y-C, et al. Anti-inflammatory effects of the partially purified extract of radix Stephania tetrandrae: comparative studies of its active principles tetrandrine and fangchinoline or human polymorphonuclear leukocyte functions. Mol Pharmacol. 2001;60:1083-90.

5. Sekiya N, et al. Suppressive effects of Stephania tetrandra of the neutrophil functions in patients with rheumatoid arthritis. Phytother Res. 2004;18:247-49.

6. Ye J, et al. On the role of hydroxyl radical and the effect of tetrandrine on nuclear factor-kappa B activation by phorbol 12-myristate 13-acetate. Ann Clin Lab Sci. 2000;30:65-71.

7. Tak P, Firestein G. NF-kB: a key role in inflammatory disease. J Clin Invest. 2001;107:7-11.

8. Hu S, et al. Potent inhibitory effect of tetrandrine on experimental allergic conjunctivitis in mice. J Ocul Pharmacol Ther. 1997;13:435-44.

9. Kim H, et al. Effects of tetrandrine and fangchinoline on human platelet aggregation and thromboxane B2 formation. J Ethnopharmacol. 1999;66:241-46.

10. Onai N, et al. Inhibiting effects of bisbenzylisoquinoline alkaloids on induction of proinflammatory cytokines, interleukin-1 and tumor necrosis factor-alpha. Planta Med. 1995;61:497-501.

11. Teh, et al. Inhibition of prostaglandin and leukotriene generation by the plant alkaloids tetrandrine and berbamine. Int J Immunopharmacol. 1990; 12:321-26.

12. Sailer E, et al. Acetyl-11-keto-[beta]-boswellic acid (AKBA): structure requirements for binding and 5-lipoxygenase inhibiting activity. Br J Pharmacol. 1996;117:615-18.

13. Uz T, et al. Aging-associated up-regulation of neuronal 5-lipoxygenase expression: putative role in neuronal vulnerability. FASEB J. 1998;12:439-49.

14. Steele V, et al. Lipoxygenase inhibitors as potential cancer chemopreventives. Cancer Epidemiol Biomarkers Prev. 1999;8:467-83.

15. Rasmark O. Editorial: 5-lipoxygenase-derived leukotrienes. Mediators also of atherosclerotic inflammation. Arterioscler Throm Vasc Biol. 2003; 23:1140-42.

16. Manev H, et al. Putative role of neuronal 5-lipoxygenase in an aging brain. FASEB J. 2000;14:1464-69.

17. Gupta I, et al. Effects of Boswellia serrata gum resin in patients with ulcerative colitis. Eur J Med. 1997;2:37-43.

18. Gupta I, et al. Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. Eur J Med Res. 1998;3:511-14.

19. Kriegelstein C, et al. Acetyl-11-keto-beta-boswellic acid, a constituent of a herbal medicine from Boswellia serrata, attenuates experimental ileitis. Int J Colorectal Dis. 2001;16:88-95.

20. Kimmatkar N, et al. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee—A randomized double blind placebo controlled trial. Phytomed. 2003;10:3-7.

21. Kotanidou A, et al. Luteolin reduces lipopolysaccharide-induced lethal toxicity and expression of proinflammatory molecules in mice. Am J Respir Crit Care Med. 2002;165:818-23.

22. Ueda H, et al. Luteolin as an anti-inflammatory and anti-allergy constituent of Perilla frutescens. Biol Pharm Bull. 2002;25:1197-1202.

23. Ueda H, et al. A hydroxyl group of flavonoids affects oral anti-inflammatory activity and inhibition of systemic tumor necrosis factor-[alpha] production. Biosci Biotechnol Biochem. 2004;68:119-25.

24. Kimata M, et al. Effects of luteolin and other flavonoids on IgE-mediated allergic reactions. Planta Med. 2000;66:25-29.

25. Kim J, et al. Inhibitory effect of luteolin on TNF-alpha-induced IL-8 production in human colon epithelial cells. Int Immunopharmacol. 2005; 5:209-17.

26. Kimata M, et al. Effects of luteolin, quercetin and baicalein on immunoglobulin E-mediated mediator release from human cultured mast cells. Clin Exp Allergy. 2000;30:501-08.

27. Shimoi K, et al. Metabolic fate of luteolin and its functional activity at focal site. Biofactors. 2000;12:181-86.

28. Shimoi K, et al. Intestinal absorption of luteolin and luteolin-7-O-beta-glucoside in rats and humans. FEBS Lett. 1998;438:220-24.

29. Klingelhoefer S, et al. Antirheumatic effect of IDS23, a stinging nettle leaf extract, on in vitro expression of T helper cytokines. J Rheumatol. 1999; 26:2517-22.

30. Broer J, Behnke B. Immunosuppressant effect of IDS30, a stinging nettle leaf extract, on myeloid dendritic cells in vitro. J Rheumatol. 2002;29:659-66.

31. Konrad A, et al. Ameliorative effect of IDS30, a stinging nettle leaf extract, on chronic colitis. Int J Colorectal Dis. 2005;20:9-17.

32. Teucher T, et al. [Cytokine secretion in whole blood of healthy subjects following oral administration of Urtica dioica L. plant extract.] Arzneimitt. 1996;46:906-10.

33. Riehemann K, et al. Plant extracts from stinging nettle (Urtica dioica), an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-kappa B. FEBS Lett. 1999;442:89-94.

34. Newmark T, Schulick P. Beyond Aspirin. Hohm Press, Prescott AZ 2000, Ch. 9.

35. Kelm M, et al. Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn. Phytomed. 2000;7:7-13.

36. Ringbom T, et al. Ursolicacid from Plantago major, a selective inhibitor of cyclooxygenase-2 catalyzed prostaglandin biosynthesis. J Nat Prod. 1998; 61:1212-15.

37. Godshani S, et al. Ocimum sanctum: an experimental study evaluating its anti-inflammatory, analgesic and antipyretic activity in animals. J Ethnopharmacol. 1987;21:153-63.

38. Archana R, Namasivayam A. Effect of Ocimum sanctum on noise induced changes in neutrophil functions. J Ethnopharmacol. 2000;73:81-85.

39. Sembulingam K, et al. Effects of Ocimum sanctum Linn on noise induced changes in plasma corticosterone level. Indian J Physiol Pharmacol. 1997;41:139-43.

40. Dona M, et al. Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis. J Immunol. 2003;170:4335-41.

41. Ahmed S, et al. Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes. Free Rad Biol Med. 2002;33:1097-1105.

42. Kundu J, et al. Inhibition of phorbol ester-induced COX-2 expression by epigallocatechin gallate in mouse skin and cultured human mammary epithelial cells. J Nutr. 2003;133:3805S-10S.

43. Wheeler D, et al. Epigallocatechin-3-gallate, a green tea-derived polyphenol, inhibits IL-1[beta]-dependent proinflammatory signal transduction in cultured respiratory epithelial cells. J Nutr. 2004;134:1039-44.

44. Aktas O, et al. Green tea epigallocatechin-3-gallate mediates T cellular NF-kB inhibition and exerts neuroprotection in autoimmune encephalomyelitis. J Immunol. 2004;173:5794-5800.

45. Hussain T, et al. Green tea constituent epigallocatechin-3-gallate inhibits COX-2 without affecting COX-1 expression in human prostate carcinoma cells. Int J Cancer. 2005;113:660-69.

46. Varilet G, et al. Green tea polyphenol extract attenuates inflammation in interleukin-2-deficient mice, a model of autoimmunity. J Nutr. 2001;131:2034-39.

47. Beyond Aspirin op cit, Ch 14.

48. Srivastava K, Mustafa T. Ginger (Zingiber officinale) and rheumatic disorders. Med Hypoth. 1989;29:25-28.

49. Jolad S, et al. Fresh organically grown ginger (Zingiber officinale): composition and effects on LPS-induced PGE2 production. Phytochem. 2004;65:1937-54.

50. Park K, et al. Inhibitor effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. Cancer Lett. 1998;129:139-44.

Depression

Continued from page 4

7. Srinivasan V, Smits M, Spence W, Lowe AD, Kayumov L, Pandi-Perumal SR, Parry B, Cardinali DP. Melatonin in mood disorders. World J Biol Psychiatry. 2006;7(3):138-51.

8. Spiegel K, Leproult R, Van Cauter E. [Impact of sleep debt on physiological rhythms] [Article in French]. Rev Neurol (Paris). 2003 Nov;159(11 Suppl):6S11-20.

9. Clement K, Covertson CR, Johnson MJ, Dearing K. St. John's wort and the treatment of mild to moderate depression: a systematic review. Holist Nurs Pract. 2006 Jul-Aug;20(4):197-203.

10. Dhikav V, Anand KS. Is hippocampal atrophy a future drug target? Med Hypotheses. 2006 Nov 10; [Epub ahead of print].

11. Sartori HE. Lithium orotate in the treatment of alcoholism and related conditions. Alcohol. 1986 Mar-Apr;3(2):97-100.

12. Nieper HA. The clinical application of lithium orotate. Agressologie. 1973;14(6):407-411.

13. Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006 Sep;163(9):1630-3.

14. Huang TL, Lin FC. High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. Prog Neuropsychopharmacol Biol Psychiatry. 2006 Oct 23; [Epub ahead of print].

15. Menegazzi M, Di Paola R, Mazzon E, Muia C, Genovese T, Crisafulli C, Suzuki H, Cuzzocrea S. Hypericum perforatum attenuates the development of carrageenan-induced lung injury in mice. Free Radic Biol Med. 2006 Mar 1;40(5):740-53.

16. Perreau VM, Bondy SC, Cotman CW, Sharman KG, Sharman EH. Melatonin treatment in old mice enables a more youthful response to LPS in the brain. J Neuroimmunol. 2006 Oct 27; [Epub ahead of print].

17. Li JH, Yu JP, Yu HG, Xu XM, Yu LL, Liu J, Luo HS. Melatonin reduces inflammatory injury through inhibiting NF-kappaB activation in rats with colitis. Mediators Inflamm. 2005 Aug 31;2005(4):185-93.

18. Kubera M, Kenis G, Bosmans E, Kajta M, Basta-Kaim A, Scharpe S, Budziszewska B, Maes M. Stimulatory effect of antidepressants on the production of IL-6. Int Immunopharmacol. 2004 Feb;4(2):185-92.

19. Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M. Anti-Inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. J Clin Psychopharmacol. 2001 Apr;21(2):199-206.

20. Aleksandrov PN, Speranskaia TV. [Dynamics of carrageenin-induced inflammation after use of lithium oxybutyrate] [Article in Russian]. Biull Eksp Biol Med. 1988 Aug;106(8):233-5.

AGEs

Continued from page 7

glycation products. Proc Natl Acad Sci U S A. 1997 Dec 9;94(25):13915-20.

7. Huebschmann AG, Regensteiner JG, Vlassara H, Reusch JE. Diabetes and advanced glycoxidation end products. Diabetes Care. 2006 Jun;29(6):1420-32.

8. Zieman SJ, Kass DA. Advanced glycation endproduct crosslinking in the cardiovascular system: potential therapeutic target for cardiovascular disease. Drugs 2004;64(5):459-70.

9. Wendt TM, Tanji N, Guo J, Kislinger TR, Qu W, Lu Y, Bucciarelli LG, Rong LL, Moser B, Markowitz GS, Stein G, Bierhaus A, Liliensiek B, Arnold B, Nawroth PP, Stern DM, D'Agati VD, Schmidt AM. RAGE drives the development of glomerulosclerosis and implicates podocyte activation in the pathogenesis of diabetic nephropathy. Am J Pathol. 2003 Apr;162(4):1123-37.

10. Koyama H, Shoji T, Yokoyama H, Motoyama K, Mori K, Fukumoto S, Emoto M, Shoji T, Tamei H, Matsuki H, Sakurai S, Yamamoto Y, Yonekura H, Watanabe T, Yamamoto H, Nishizawa Y. Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol. 2005 Dec;25(12):2587-93. Epub 2005 Oct 13.

11. DeGroot J, Verzijl N, Wenting-van Wijk MJ, Jacobs KM, Van El B, Van Roermund PM, Bank RA, Bijlsma JW, TeKoppele JM, Lafeber FP. Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis Arthritis Rheum. 2004 Apr;50(4):1207-15.

12. Sato T, Shimogaito N, Wu X, Kikuchi S, Yamagishi S, Takeuchi M. Toxic advanced glycation end products (TAGE) theory in Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2006 Jun-Jul;21(3):197-208.

13. Pokupec R, Kalauz M, Turk N, Turk Z. Advanced glycation endproducts in human diabetic and non-diabetic cataractous lenses. Graefes Arch Clin Exp Ophthalmol. 2003 May;241(5):378-84. Epub 2003 Apr 16.

14. Hein G, Franke S. Are advanced glycation end-product-modified proteins of pathogenetic importance in fibromyalgia? Rheumatology (Oxford). 2002 Oct;41(10):1163-7.

15. Diamanti-Kandarakis E, Piperi C, Kalofoutis A, Creatsas G. Increased levels of serum advanced glycation end-products in women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2005 Jan;62(1):37-43.

16. Taguchi A, Blood DC, del Toro G, Canet A, Lee DC, Qu W, Tanji N, Lu Y, Lalla E, Fu C, Hofmann MA, Kislinger T, Ingram M, Lu A, Tanaka H, Hori O, Ogawa S, Stern DM, Schmidt AM. Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases. Nature. 2000 May 18;405(6784):354-60.

17. Hipkiss AR. Would carnosine or a carnivorous diet help suppress aging and associated pathologies? Ann N Y Acad Sci. 2006 May;1067:369-74.

18. Stuerenburg HJ. The roles of carnosine in aging of skeletal muscle and in neuromuscular diseases. Biochemistry (Mosc) 2000 Jul;65(7):862-5.

19. Peterszegi G, Molinari J, Ravelojaona V, Robert L. Effect of advanced glycation end-products on cell proliferation and cell death. Pathol Biol (Paris). 2006 Sep;54(7):396-404. Epub 2006 Aug 21.

20. Muller H, Reinwein H. Pharmacology of galegin. Arch Expll Path Pharm. 1927; 125:212-28.

21. Khatami M, Suldan Z, David I, Li W, Rockey JH. Inhibitory effects of pyridoxal phosphate, ascorbate and aminoguanidine on nonenzymatic glycosylation. Life Sci. 1988;43(21):1725-31.

22. Leklem JE, Hollenbeck CB. Acute ingestion of glucose decreases plasma pyridoxal 5'-phosphate and total vitamin B-6 concentration. Am J Clin Nutr. 1990 May;51(5):832-6.

23. Booth AA, Khalifah RG, Hudson BG. Thiamine pyrophosphate and pyridoxamine inhibit the formation of antigenic advanced glycation end-products: comparison with aminoguanidine. Biochem Biophys Res Commun. 1996 Mar 7;220(1):113-9.

24. Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med. 2003 Mar;9(3):294-9. Epub 2003 Feb 18.

25. Arora S, Lidor A, Abularrage CJ, Weiswasser JM, Nylen E, Kellicut D, Sidawy AN. Thiamine (Vitamin B(1)) Improves Endothelium-Dependent Vasodilatation in the Presence of Hyperglycemia. Ann Vasc Surg. 2006 May 31; [Epub ahead of print]

26. Hassinger W, Sauer G, Cordes U, Krause U, Beyer J, Baessler KH. The effects of equal caloric amounts of xylitol, sucrose and starch on insulin requirements and blood glucose levels in insulin-dependent diabetics. Diabetologia. 1981 Jul;21(1):37-40.

27. McPherson JD, Shilton BH, Walton DJ. Role of fructose in glycation and cross-linking of proteins. Biochemistry. 1988 Mar 22;27(6):1901-7.

28. Levi B, Werman MJ. Long-term fructose consumption accelerates glycation and several age-related variables in male rats. J Nutr. 1998 Sep;128(9):1442-9.

29. Nangaku M, Izuhara Y, Usuda N, Inagi R, Shibata T, Sugiyama S, Kurokawa K, van Ypersele de Strihou C, Miyata T. In a type 2 diabetic nephropathy rat model, the improvement of obesity by a low calorie diet reduces oxidative/carbonyl stress and prevents diabetic nephropathy. Nephrol Dial ransplant. 2005 Dec;20(12):2661-9. Epub 2005 Sep 27.

PET CORNER

By Gary L. Ailes, DVM

Omega-3 Fatty Acids in Our Pets

As the shift in weather continues and the air turns a bit more towards bitter, we may find our pets spending more time inside. The question that comes to mind is what can we do to help protect their health while indoors?

One simple food additive would be the use of flax seed oil or, better yet, ground fresh flax seeds. Flax seeds provide a high level of omega-3 fatty acids, which are usually scarce in the diet. Flax seeds also have omega-6 and omega-9 fatty acids as well.

Essential fatty acids are required for normal brain development, cell membrane and hormone formation, metabolism of cholesterol and triglycerides, and cellular energy production. They also serve as precursors to prostaglandins. In addition, essential fatty acids have been used to decrease arthritic pain by blocking inflammation. Flax seed oil is an excellent immune modulator and helps to improve immunity in diseases such as lupus. Like in humans, in pets, the omega-3 fatty acids are metabolized into anti-inflammatory products. The omega-6 fatty acids can either follow the same process or enter the inflammatory cascade.

It is necessary for pets to have both of these essential fatty acids to function normally. If there are not enough omega-3s our pets experience too much inflammation. If there are not enough omega-6s there is not enough stiffness in the vascular system to maintain normal blood pressure. Considering the normal diet of most pets, adding more omega-3 fatty acids is definitely an ideal way to improve health.

When deciding to add flax seed oil or ground flax seeds to your pet's diet, we must remember that flax seed oil must be cold pressed, needs to come from a very reliable source, must be stored in the refrigerator and must be used within 6 weeks of the time the bottle is opened. High quality flax seed oil is a good choice if the contents of the bottle are to be used fast enough.

The other option is to use ground flax seeds. The seeds perfectly encapsulate the oil contained within and have other beneficial constituents. The balance of other materials makes the seed a great choice. They must be ground in order to release the benefit of the oil and fiber. There is both absorbable and non-absorbable fiber contained within the seeds and both provide benefits to our pets' bodies.

To read the rest of this article please go to www.vrppet.com

Resveratrol Improves Health and Survival of Mice on a High-Fat Diet

A new study in the journal *Nature* indicates that high doses of resveratrol offset the damaging effects of a high-fat diet and extends the lifespan of middle-aged mice. The results of the study were widely reported in conventional media sources such as the *New York Times* and the *San Francisco Chronicle* and further confirm past studies reported by *VR News* on resveratrol's potential life-extending effects in yeast and fruit flies.

In the current study, the researchers fed one group of mice a diet containing 60 percent of calories from fat from the time the animals were middle aged (1 years old). The mice developed signs of pre-diabetes, had enlarged livers, and died much sooner than mice fed a standard diet. Researchers fed another group of animals the same high-fat diet combined with a large daily dose of resveratrol.

Results indicated that although the resveratrol group still gained weight like the other mice on a high-fat diet, resveratrol shifted the physiology of middle-aged mice towards that of mice on a standard diet and significantly increased their survival. Resveratrol produced changes associated with longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-I) levels, and increased mitochondrial number. Resveratrol opposed the effects of the high-fat diet in 144 out of 153 pathways that the high-fat diet altered. Resveratrol-fed animals that also consumed the high-fat diet died a number of months later than the mice on the high-fat diet alone. The resveratrol mice died at the same rate as the mice on a standard healthy diet.

In the resveratrol group, there also were no signs of the enlarged livers seen in mice on a high-fat diet that did not consume the red-wine derived component. Another effect experienced by the resveratrol group was improved motor function. To test this effect, the scientists had the mice walk along a rotating rod. As they grew older, the resveratrol mice did better on the test and stayed on the rod nearly as long as those animals fed a normal diet.

The scientists fed the animals 24 milligrams of resveratrol per kilogram of body weight. Red wine contains about 1.5 to 3 milligrams of resveratrol per liter. Consequently, a 150-pound person would need to consume from 1,500 to 3,000 bottles of red wine a day to obtain an equivalent dose.

According to the researchers, "These data show that improving general health in mammals using small molecules is an attainable goal, and point to new approaches for treating obesity-related disorders and diseases of ageing."

Reference:

Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, et. al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006 Nov 1; [Epub ahead of print]

VRP's resveratrol capsules contain 20 mg of resveratrol.

Vitamin C May Increase Fertility

Vitamin C increases sperm count in infertile men and improves other aspects of sperm health, a new study indicates.

In the study, researchers measured sperm motility, sperm count, and sperm morphology (structure and form of the sperm) before and after vitamin C treatment in 13 infertile patients ranging in age between 25 and 35 years. The subjects were free from genital infections. Physical examination and other routine laboratory investigations were normal.

The subjects received 1,000 mg of vitamin C twice per day for a maximum of 2 months. Results showed that the mean sperm count was increased after 2 months of vitamin C intake. The mean sperm motility increased significantly and mean sperms with normal morphology increased significantly after vitamin C treatment.

The researchers concluded, "This study showed that vitamin C supplementation in infertile men might improve sperm count, sperm motility, and sperm morphology and might have a place as an additional supplement to improve the semen quality towards conception."

Reference:

Akmal M, Qadri JQ, Al-Waili NS, Thangal S, Haq A, Saloom KY. Improvement in Human Semen Quality After Oral Supplementation of Vitamin C. Journal of Medicinal Food. 2006 September;9(3):440-42.

Turmeric Component May Act as Cognitive Enhancer

Curcumin, the pigment responsible for turmeric's yellow color, helps immune cells clear out the plaque build-up that is thought to play a role in Alzheimer's disease, a new study indicates.

Alzheimer's disease patients have defects in phagocytosis, the process immune cells use to "gobble up" amyloid-beta, plaque deposits in the brain that are associated with Alzheimer's. They also have defects in their body's ability to clear amyloid-beta plaques. In animal experiments, curcumin enhanced brain clearance of amyloid-beta. Consequently, in the current study, scientists treated immune cells (macrophages) from six Alzheimer's patients and three controls with curcumin in vitro and measured amyloid-beta uptake.

At baseline, the intensity of amyloid-beta uptake by the macrophages from Alzheimer's patients was significantly lower in comparison to control macrophages. After treatment of macrophages with the curcumin compound, amyloid-beta uptake by macrophages from three of the six Alzheimer's patients was significantly increased.

The age of the patient and the stage of the Alzheimer's disease appeared to influence the effectiveness of curcumin. The most benefit occurred in the cells from younger patients and patients with early-stage Alzheimer's. The curcumin appeared

to have no effect on the macrophages from the healthy controls.

According to the researchers, "Immunomodulation of the innate immune system by curcuminoids might be a safe approach to immune clearance of amyloidosis in [the] Alzheimer's disease brain."

Reference

Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M, Zaghi J, Badmaev V, Graves MC, Bernard G, Rosenthal M. Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients. J Alzheimers Dis. 2006 Nov;10(1):1-7.

Cinnamon Linked to Heart and Insulin Health

A new placebo-controlled, double-blind study indicates Cinnulin PF®, a special cinnamon extract, may act as an antioxidant to reduce oxidative stress linked to the metabolic syndrome.

The metabolic syndrome is a condition characterized by central obesity, hypertension, and disturbed glucose and insulin metabolism. The syndrome has been linked to increased risks of both type-2 diabetes and cardiovascular disease.

The study, presented at the 47th American College of Nutrition annual meeting, is thought to be the first to show cinnamon's effect in humans and adds further support to studies showing that cinnamon has a positive effect on glucose metabolism.

In the placebo-controlled, double-blind trial, researchers from the Joseph Fourier University in France studied 24 subjects with impaired fasting glucose. The subjects were randomly assigned to receive either a daily dose of 500 milligrams of cinnamon extract (Cinnulin PF) or a placebo for 12 weeks.

At the end of the study the researchers found that markers of plasma antioxidant levels were significantly increased in the cinnamon group relative to the placebo group. In addition, plasma levels of a compound that is a marker of oxidative stress (malondialdehyde) were decreased in the cinnamon group, but remained unchanged in the placebo group.

The authors concluded that cinnamon extract's active compounds may be helpful in reducing the risk of heart disease and diabetes by protecting cells from harmful oxidation.

A previous study in 2003 by one of this trial's lead researchers (Diabetes Care. 26:3215-3218) reported that just 1 gram of cinnamon per day reduced blood glucose levels, triglycerides, LDL cholesterol, and total cholesterol in a small number of subjects with type 2 diabetes. Another placebo-controlled, double-blind study (Journal of the American College of Nutrition. 2006;25:144-150) found that cinnamon and Cinnulin PF could reduce blood pressure in spontaneously hypertensive rats.

Cinnulin PF contains standardized quantities of the active components of cinnamon, two trimers and one tetramer classified as double-linked type-A polymers, but omits compounds that are potentially harmful when cinnamon is consumed at high doses.

Reference:

Roussel AM, Anderson R, et. al. The 47th American College of Nutrition annual meeting. October 2006.

Folic Acid—Even at Low Doses—May Lower Homocysteine

Low-dose folic acid supplementation reduces homocysteine concentration in coronary artery disease patients with high homocysteine levels, a new study from Taiwan indicates.

High levels of the amino acid homocysteine are considered a marker for heart disease. Emerging research also indicates that higher homocysteine levels are associated with dementia. Research indicates that folic acid as well as vitamins B6 and B12 can lower homocysteine levels.

Researchers sought to determine whether patients with coronary artery disease need to supplement their diet with a high dose of folic acid (even if their folate status is adequate) to reduce their plasma homocysteine concentration or whether a low dose of the supplement would be equally effective.

In the two-month study, 22 patients were randomly assigned to a placebo group while 24 patients were assigned to a folic acid group (400 micrograms per day).

In those subjects who did not have high homocysteine levels, folic acid supplements did not significantly lower fasting plasma homocysteine concentration. However, low-dose folic acid supplementation significantly reduced homocysteine at week 8 for those subjects with high homocysteine levels.

The researchers also examined folic acid's effects in subjects with potential genetic defects in the metabolic pathway of homocysteine. People who have this genetic defect along with low folate status are reported to have higher homocysteine concentrations than people who do not have the mutation. When people with this genetic defect were given low-dose folic acid supplementation for eight weeks, they experienced a significant drop in homocysteine levels.

Past studies have reported that vitamin B12 is more important than folate in determining homocysteine levels in people over age 70, indicating folic acid should be used in conjunction with other homocysteine lowering vitamins. Some scientists have called for future studies to investigate the effect of 1,000 micrograms of B12 in elderly people.

Reference:

Lina PT, Leeb B-J, Changc H-H, Chenga C-H, Tsaid A-J, Huanga YC. Low-dose folic acid supplementation reduces homocysteine concentration in hyperhomocysteinemic coronary artery disease patients. Nutrition Research. September 2006; 26(9):460-466.

Be sure to read *The President's Desk* for important product information.

Vitamin Research News

Dedicated to the Scientific Pursuit of Better Health

DECEMBER 2006 | Vol. 20, Number 12 | $29.95/Year U.S. ($39.95/Year International)

In This Issue:

4610 Arrowhead Drive, Carson City, NV 89706

An Employee Owned Company

Vitamin Research Products

Since 1979

PRSRT STD
U.S. POSTAGE
PAID
PERMIT #625
RENO, NV

Printed in the U.S.A.