The Uses and Benefits of Alpha Lipoic Acid

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Alpha Lipoic Acid, or thioctic acid, is a sulfur-containing fatty acid compound that acts as a co-enzyme and an antioxidant. It is called a "universal antioxidant" because of its potent ability to neutralize a wide range of free radicals. Recent studies suggest that alpha lipoic acid may improve situations in the body involving free radicals, such as heart disease and cancer, and other disorders associated with inflammation and aging. The uses and benefits of alpha lipoic acid are numerous, making it an important nutrient for maintaining and regaining health in the 21st century.

History

Alpha lipoic acid was first isolated in 1951 by biochemist, Lester Reed Ph.D. Dr. Reed purified a very small amount of alpha lipoic acid crystals from a sample of liver that weighed 250 pounds.[1] Alpha lipoic acid is a naturally occurring compound that is produced in small amounts by plants, animals, and humans.[2] It was found to be a co-factor for several mitochondrial enzyme complexes that are involved in energy production, similar in function to many of the B vitamins.[3] But unlike the B vitamins, alpha lipoic acid was not classified as a vitamin because it is able to be synthesized by the body. Alpha lipoic acid is found in abundance in animal tissues with high metabolic activity, such as kidney, heart, and liver, and to a lesser extent in fruits and vegetables. Non-animal sources are spinach, broccoli, tomatoes, peas, brussel sprouts, and rice bran. All alpha lipoic acid supplied by the diet is transported in the bloodstream to tissues and incorporated into cells. It is then transferred into the mitochondria. Studies in mammals have shown the alpha lipoic acid supplied by the diet does not supply enough for purposes such as incorporation into enzyme complexes.[4] Hence, these sources of alpha lipoic acid are thought to provide very little free alpha lipoic acid into circulation. It is only through supplementation that alpha lipoic acid reaches potentially therapeutic levels.

Alpha lipoic acid works on the cellular level to help produce energy in the body. To do this, it acts as a coenzyme in the energy cycle of the cell, called the citric acid cycle. The conversion of food to energy is driven by a series of chemical reactions that are set in motion by enzymes. Alpha lipoic acid takes a part in this multienzyme process by preparing the fuel for the mitochondria, the power plants of the cell, and plays a vital role in mitochondrial electron transport reactions required for metabolizing glucose into adenosine triphosphate, or ATP, for cellular energy production.[5]

Alpha lipoic acid is a medium chain fatty acid with two sulfur atoms. The reduced form is known as dihydro-lipoic acid and the oxidized form is known as alpha lipoic acid. Alpha lipoic acid also contains an asymmetric carbon, which means that there are two possible optical isomers that are mirror images of each other: R-lipoic acid and S-lipoic acid. R-lipoic acid is a natural form of alpha lipoic acid, while S-lipoic acid is the synthetic form. It is the natural form of alpha lipoic acid that has been found to have the greatest benefit to the body. Researchers have found that synthetic alpha lipoic acid does not improve ATP synthesis in isolated cells like the natural form does. And the natural R-form was shown to increase membrane fluidity and transport, while the S-form was much less effective in doing so.[6] The reduced form has been found to exert a number of antioxidant and neuro-protective actions that are not seen in alpha lipoic acid. While both forms are able to scavenge a number of free radicals, only R-dihydro-lipoic acid has been shown effective against superoxide and peroxyl reactive oxygen species.[7]

The oxidized and reduced forms of R-lipoic acid made up a redox couple. Oxidation reduction or redox reactions involve the transfer of an electron from a donor to an acceptor. This transfer changes the reduced form to the oxidized form when the donor loses an electron. When an acceptor gains an electron, it changes from its oxidized form to its reduced form. It is through this cycle of reduction to R-dihydrolipoic acid and oxidation back to R-lipoic acid that beneficial processes take place, such as the ability to provide cysteine, an amino acid that is critical for glutathione production.[8]

It is the R-form of alpha lipoic acid that occurs naturally in foods, covalently bound to lysine in proteins, such as beef liver. Because the content of alpha lipoic acid in foods is limited, dietary supplements are likely as much as 1000 times greater than the amounts that could be obtained through the diet. In the United States, alpha lipoic acid is available without a prescription and has been available since the 1990's.[9] Most alpha lipoic acid supplements contain a 50/50 mixture of R-lipoic acid and S-lipoic acid. There are a few companies that offer the R-form of alpha lipoic acid, but it more expensive than alpha lipoic acid. Direct comparisons of the bioavailability of the 50/50 mixture and R-lipoic acid supplements have not been published. However, a few studies have found that after oral dosing with the 50/50 mixture of the R-lipoic acid and the S-lipoic acid, peak plasma concentrations of the R-form were found to be 40-50% higher than the S-form, suggesting that R-lipoic acid is better absorbed than S-lipoic acid.[10] [11]

Benefits

Alpha lipoic acid has a wide range of benefits. The most important benefit is its role as an

antioxidant. In 1988, the antioxidant properties of alpha lipoic acid were discovered. It was shown to have powerful antioxidant abilities, equal to that of coenzyme Q 10, vitamin C, and vitamin E.[12] Free radicals are highly unstable electrons that are a normal byproduct of oxidative metabolism. But when they get out of control, these electrons can cause extensive damage to lipid membranes, organelles, and to DNA itself. Unlike other antioxidants, alpha lipoic acid has the unique ability to neutralize free radicals within aqueous and lipid regions of the cells, as well as in intracellular and extracellular environments.[13] This ability allows alpha lipoic acid to be easily transported across cellular membranes to neutralize free radicals. Vitamin C is only able to protect the watery portions of cells from free-radical attack, and vitamin E is only able to protect the fatty membranes. But alpha lipoic acid has the ability to neutralize free radicals that occur in both the watery and fatty regions of the cell. Alpha lipoic acid is capable of neutralizing a wide variety of free radicals, such as singlet oxygen, superoxides, peroxyl and hydroxyl radicals, hypochlorite, and peroxynitrite.[14] Other antioxidants, like vitamin C, vitamin E, or glutathione can only neutralize one kind of free radical. Researchers call alpha lipoic acid the "universal antioxidant" because it can neutralize such a wide variety of free radicals.

Not only is alpha lipoic acid able to neutralize free radicals, it is also able to recycle or regenerate several other important antioxidants, including vitamin C and glutathione. When an antioxidant scavenges a free radical, it becomes oxidized in the process and is not able to scavenge additional free radicals until is has been reduced. The reduced form of alpha lipoic acid, dihydro-lipoic acid, is able to reduce the oxidized antioxidants, enabling them to be useful again.[15] Increasing glutathione levels is very important because it is one of the body's most important intracellular antioxidants. Gluthathione is a compound that is composed of 3 amino acids: cysteine, glutamic acid, and glycine. It protects the body from free radical damage and plays a leading role in the detoxification and elimination of potential carcinogens and toxins in the body. Glutathione conjugation is one of the primary mechanisms for eliminating xenobiotics in the liver.[16] Animal studies have shown that glutathione synthesis and cellular glutathione levels are significantly lower in aged animals than in younger animals, leading to a decreased ability of aged animals to respond to toxin exposure and oxidative stress.[17]

Alpha lipoic acid, when fed to the aged animals, has been found to increase glutathione synthesis in cultured cells and in animal tissues.[18] In a study with rats, oral dosing of 150 mg/kg/day for eight weeks significantly increased the glutathione levels in the blood and in the liver.[19] Increases in glutathione levels that alpha lipoic acid provides are not only from the reduction of oxidized glutathione, but also from the synthesis of glutathione. [20] The availability of cysteine inside a cell determines its rate of glutathione synthesis. Alpha lipoic acid, by its reduction to dihydro-lipoic acid and oxidation back to alpha lipoic acid, has the ability to continuously provide cysteine, an important amino acid for glutathione production. It reduces

extracellular cystine to cysteine and increases the uptake of cysteine into the cell, increasing glutathione production. [21]

Alpha lipoic acid has been found to reduce the formation of glycosylated end products, or AGEs.[22] AGEs are formed when proteins react with sugars, and this process increases the risk of cardiovascular disease by oxidizing LDL cholesterol and making blood vessels tough and inflexible. It can also affect the left ventricle of the heart, reducing its ability to pump blood into the circulation, and increasing blood pressure. Glycosylated proteins are also unable to bind to receptors on liver cells to signal the cessation of cholesterol manufacturing. This causes the body to continue to produce too much cholesterol. Alpha lipoic acid stops these processes from happening by inhibiting glycation at the starting point.[23] In a study with rats, the effect of alpha lipoic acid was investigated on the formation of AGEs. The rats were given a glucose solution to drink for 4 weeks, combined with a normal chow diet or a diet supplemented with alpha lipoic acid. The chronic administration of the glucose resulted in a 29% increase in blood pressure, 30% increase in glycemia, 286% increase in insulinemia, 408% increase in insulin resistance index, and a 63% increase in AGE content in the aorta. The rats that were given alpha lipoic acid did not have the increases in blood pressure, insulin levels, insulin resistance, and aorta AGE content. By preventing AGE formation, alpha lipoic acid prevented the development of hypertension and hyperglycemia in the rats.[24]

Another benefit of alpha lipoic acid is its ability to chelate, or bind, with heavy metals. Both forms of alpha lipoic acid have been shown to form complexes with manganese, zinc, cadmium, lead, cobalt, nickel, and iron ions.[25] In one study, an intraperitoneal injection of 25 mg/kg alpha lipoic acid given to rats for seven days was able to significantly alter the oxidative stress caused by lead toxicity.[26] In another study, alpha lipoic acid was demonstrated to be able to protect rat hepatocytes from cadmium toxicity by preventing decreases in total glutathione and increases in lipid peroxidation.[27] These protective effects have also been seen in rats who had depleted levels of glutathione prior to cadmium exposure.[28] A study with rats examined the effects of alpha lipoic acid on arsenic toxicity. Arsenic toxicity caused decreases in glutathione peroxidase in the brain of the rats, decreased activity of superoxide dismutase, and decreased catalase activity. All regions of the brain also showed increased levels of reactive oxygen species and other intracellular oxidants and an increase in lipid peroxidation levels. Rats that were given alpha lipoic acid simultaneously to the arsenic did not demonstrate the deficits in antioxidant enzyme activities or the increase in lipid peroxidation. Alpha lipoic acid was able to prevent arsenic-induced changes in the antioxidant defense system of the rats.[29] Alpha lipoic acid has also been found to protect against chromate induced oxidative stress in mouse liver.[30] While other chelators such as dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulfonic acid (DMPS) are unable to cross the blood-brain barrier and remove heavy metals from the brain, alpha lipoic acid is particularly suited to this purpose as it can penetrate both the blood-brain barrier and the cell membrane.[31] [32]

Protection from irradiation is another benefit of alpha lipoic acid. Studies have evaluated the effects of alpha lipoic acid on radiation injury in both animals and humans. In mice, it has been demonstrated that alpha lipoic acid, but not dihydro-lipoic acid, was able to protect against radiation injury to cells involved in blood cell formation. Administration of alpha lipoic acid increased the survival rate of irradiated mice from 35% in untreated animals to 90% in treated animals. [33] In a Russian study involving Chernobyl radiation victims, alpha lipoic acid was shown to greatly reduce free radical damage caused by the radiation exposure. A group of 16 children given 400 mg of alpha lipoic acid for 28 days had significant reduction in both white blood cell free radical activity and urinary excretion of radioactive isotopes compared to a control group. Alpha lipoic acid lowered levels of chemiluminescence, a marker for lipid peroxidation, to levels of children who were not exposed to radiation. Combining vitamin E with alpha lipoic acid further reduced chemiluminescence to below normal levels. Vitamin E alone did not have this effect. Kidney and liver function was also normalized by the alpha lipoic acid treatment.[34]

Alpha lipoic acid has demonstrated the ability to protect the liver from poisons and the ability to regenerate the liver if it has already been damaged. Some of the first human clinical studies using alpha lipoic acid were carried out by Fredrick C. Bartter and Burton M. Berkson from the National Institutes of Health in the 1970's. Intravenous alpha lipoic acid was administered to 79 people with acute and severe liver damage at several medical centers in the United States and 75 people recovered full liver function.[35] Dr. Berkson has since used it successfully for the treatment of many chronic liver diseases, such as viral hepatitis and autoimmune hepatitis.[36] Alpha lipoic acid infusions were used in the treatment of potentially deadly amanita mushroom poisoning in 75 patients between 1974 and 1978. 89 percent of the patients recovered after receiving the lipoic acid infusion, while only 10-50 percent of patients recovered without intervention. [37] Alpha lipoic acid's ability to regenerate the liver is demonstrated in a study of three people with liver damage from Hepatitis C. Through the use of alpha lipoic acid, selenium, and silymarin, all three were able to avoid liver transplants and regained liver function.[38]

Alpha lipoic acid has a beneficial effect on cholesterol and lipid levels. One study, which explored the effect of antioxidant capacity on blood lipid metabolism and lipoprotein lipase (LPL) activity of rats fed with a high-fat diet, found that alpha lipoic acid improved the antioxidant capacity and activity of LPL and reduced blood lipids significantly. [39] In a study with mice fed a high fat diet, supplementation with alpha lipoic acid caused a decrease in lipid peroxidation, plasma cholesterol, triglycerides, and low-density lipoprotein cholesterol, and an increase in high-density lipoprotein cholesterol. [40] The effect of alpha lipoic acid on lipid peroxidation and lipid levels has been studied in the blood, liver, and kidneys of young and aged rats. Lipid

levels were considerably higher in the aged rats compared with the young rats. Alpha lipoic acid was administered intraperitoneally for 7 and 14 days. It was shown to prevent the elevated lipid levels seen in the aged rats.[41]

Alpha lipoic acid has been found to prevent calcium oxalate crystals or stones from forming and damaging the kidneys. Hyperoxaluria is the excretion of an excessive amount of oxalate in the urine and the major risk factor for the formation of urinary calcium oxalate stones. In a study with rats, alpha lipoic acid and eicosapentaenoic acid (EPA) were shown to reduce tubular damage and decreased the markers of crystal deposition substantially in the animals. The EPA and alpha lipoic acid was effective at inhibiting stone formation and was able to protect the kidneys from damage caused by oxalate toxicity.[42]

Nuclear factor kappa beta is a transcription factor. Transcription factors are messengers found inside the cell, and they carry information from the cytoplasm to the nucleus. They activate or inhibit the production of certain proteins or enzymes, which then carry out a particular cell function. Nuclear factor kappa beta is an inflammatory messenger which turns on inflammation. By stabilizing nuclear factor-kappa B transcription factors in the body, alpha lipoic acid can regulate a number of genes that are related to inflammation and cell cycle control, which are involved in the pathology of diabetes, atherosclerosis, and cancer.[43] Th1- and Th2-mediated immune system cells identify and respond to oxidative stress with certain cell membrane receptors. These receptors initiate a cascade of events that eventually activate the master transcription factor NF-kappa B. NF-kappa B is then able to bind to DNA and affect the rate of transcription of certain deleterious genes. Because of this, NF-kappa B plays a significant role in the regulation of inflammatory-induced gene function. High doses of alpha lipoic acid have been shown to inhibit the activation of NF-kappa B when added to cell culture.[44] Because of this ability, alpha lipoic acid has been used for the treatment of various cancers for which no effective treatments exist. Dr. Berkson used intravenous alpha lipoic acid, low dose naltrexone, and other oral antioxidants to achieve long term survival of a patient with metastasized pancreatic cancer.[45] Another case study, published in 2007, described the complete reversal of a B-cell lymphoma in a patient using less than one month of intravenous alpha lipoic acid and six months of low dose naltrexone. [46]

Alpha lipoic acid also displays antihyperglycemic effects.[47] It has been shown to aid in increasing glucose uptake in skeletal muscles as well as improving insulin-stimulated glucose disposal. [48] Alpha lipoic acid works against insulin resistance by increasing the permeability of cell membranes, which is decreased in hyperglycemia. [49] A study was done on the effect of alpha lipoic acid on insulin sensitivity in people with type 2 diabetes mellitus. Twelve patients were given an oral 600 mg tablet of alpha lipoic acid twice a day, one tablet in the

morning and the other in the evening, 30 minutes before the meal, for a period of 4 weeks. Insulin sensitivity was measured using a manual hyperinsulinaemic euglycaemic clamp technique. The 4-week treatment with alpha lipoic acid significantly improved glucose utilization in the type 2 diabetic patients. In half of the patients, the amount of glucose metabolized after the treatment reached a level considered normal for healthy people. [50]

Another significant benefit of alpha lipoic acid lies with the mitochondria. Mitochondria are cellular organelles that oxidize dietary proteins, fats, and carbohydrates into a useable form of energy, called adenosine triphosphate, or ATP. Mitochondria provide energy for basic metabolic processes, and their decay with age impairs cellular metabolism and leads to decline of cellular function. Mitochondrial dysfunction appears to contribute to some of the loss of function accompanying aging because aged tissue uses oxygen inefficiently, which impairs ATP synthesis, resulting in increased free radical production.[51] The high amount of oxidants not only damages the mitochondria, but it may eventually cause inadequate energy production and the general metabolic decline evident in aging. In a study using old rats, it was found that supplementing with 0.5% R-lipoic acid for 2 weeks partially reversed the age-associated loss of mitochondrial function, the increase in oxidative stress, and the damage and decline in general metabolic activity. The supplemented rats were significantly more active, which further shows that (*R*)-lipoic acid acts physiologically to increase general metabolic activity.[52]

Systemic inflammation plays an important role in several diseases. Alpha lipoic acid has also been found to have significant benefits on inflammation due to its ability to down regulate pro-inflammatory cytokines. When free radicals disrupt the normal structure of proteins and the genetic information encoded in DNA, this damage always results in the release of potent chemical messengers called cytokines. Cytokines trigger the inflammatory response in tissues, signaling immune and inflammatory cells to swarm the affected area. Lipoic acid inhibits prostaglandin E2 production by inhibiting COX 2 activity.[53] Another study investigated the prophylactic effect of alpha lipoic acid on systemic inflammation in mice. The mice were divided into 3 groups: control, systemic inflammation, and alpha lipoic acid treated mice with systemic inflammation. Mice with systemic inflammation had higher levels of reactive oxygen species in lymphocytes, hepatocytes, and astrocytes than the control mice. However, the mice receiving the alpha lipoic acid did not show elevated levels of the reactive oxygen species. Systemic inflammation also increased levels of lipid peroxidation and decreased levels of superoxide dismutase, catalase, glutathione peroxidase, and glutathione. These levels were reduced to almost normal levels when the mice were treated with alpha lipoic acid.[54]

Stress is a stimulus that can alter physiological homeostasis and can cause many physiological changes in the body. The ability to cope with stress is a crucial determinant of health and dis-

ease.[55] There have been studies that have indicated that long-term exposure to stress has a detrimental effect on several brain functions and increases the production of free radicals in the body.[56] Stress has been shown to cause depletion of the glutathione-based antioxidant defense system of the body and to decrease the level of vitamin C in the body.[57] In a study with rats, the effect of stress on lipid peroxidation and decreased antioxidant enzymes in the retina and brain were specifically examined. The researchers found that stress caused a significant decrease in brain copper/zinc superoxide dismutase and the levels of glutathione peroxidase in the brain and retina. Rats given alpha lipoic acid while being exposed to stress were protected from lipid peroxidation by the antioxidant properties of alpha lipoic acid. [58] Alpha lipoic acid might provide indirect benefit when cortisol levels are high because it can partially restore the hydrocortisone-induced suppression of helper T-cell activity.[59] It has also been shown to prevent the accumulation of catecholamines in cardiac tissue in response to stress and to enhance the elimination of catecholamine degradation products.[60]

Due to the broad range of health benefits alpha lipoic acid is able to provide, it has been used in the treatment of many chronic degenerative diseases. The biological activities of alpha lipoic acid make it an important supplement with the potential for both preventing and treating disease. It has been shown to have a beneficial effect on many different diseases, from cataracts to cancer.

Because cataracts are associated with reduced antioxidant activity in the lens of the eye, alpha lipoic acid has been shown in animal studies to inhibit cataract formation. Research has shown that lenses with cataracts have dramatic decreases in reduced glutathione, as much as 81 percent, when compared with normal lenses.[61] Results of one rat study showed that 25 mg/kg body weight of alpha lipoic acid protected 60 percent of the animals from cataract formation. The major biochemical changes in the lens associated with the protective effect of alpha-lipoic acid were increases in glutathione, ascorbate, and vitamin E levels.[62] The researchers in this study found that the reduced form of alpha lipoic acid, R-dihydro-lipoic acid, reached higher concentrations in the rat lenses than the synthetic form of alpha lipoic acid. [63] This data demonstrated that R-lipoic acid was more effective in maintaining glutathione levels and protecting the lens from damage than the S-lipoic acid.

Low levels of glutathione may also contribute to the pathological processes in the development of glaucoma. Supplementation of alpha lipoic acid has been shown to increase glutathione in red blood cells and the lacrimal fluid of patients with glaucoma.[64] In a Russian trial of alpha lipoic acid, 45 patients with stage I and II glaucoma were given either 75 mg or 150 mg for 2 months. A control group of glaucoma patients was given only local hypotensive medication. Improvement was seen in 45 percent of those patients receiving alpha lipoic acid. [65]

The antioxidant properties of alpha lipoic acid make it beneficial for reversing the aging process. There is a declining ability with age to respond to oxidative stress. Oxidative stress is a condition that arises when our cells cannot adequately destroy the free radicals that are a normal byproduct of cellular processes. Oxidative stress also results from exposure to toxic chemicals such as pesticides, hydrocarbons, smog, alcohol, and prescription drugs. During the aging process, there is an increase of mitochondrial decay,[66] oxidant production, and oxidative damage to important molecules.[67] These processes may in part be responsible for aging as well as age-associated degenerative diseases such as cancer and atherosclerosis.[68] In one study, researchers from the University of California at Berkeley took liver cells from aging rats and measured their energy level, free radical level, and the ability of the cells to recycle vitamin C. The aged rats were 3 times less active than the young rats. The free radicals were 5 times higher in the aged rats, the energy production was very low, and the ability to recycle vitamin C in the aged rats was only half of the levels of the young rats. After 2 weeks on R-lipoic acid, free radicals decreased, vitamin C levels rose, and energy levels rose significantly. Glutathione levels also increased when the aged rats were given alpha lipoic acid. Improvement in metabolic activity as well as lowering oxidative stress and the damage caused by aging were significantly improved by the use of alpha lipoic acid. [69] With age, glutathione levels naturally decline, making older animals more vulnerable to both free radicals and other environmental toxins. Another study with rats examined the effect of alpha lipoic acid and acetyl-L-carnitine on age-related decline in metabolic function and oxidative stress. The combination was able to partially reverse the decline in average mitochondrial membrane potential and significantly increased the ambulatory activity in both the young and old rats. Levels of vitamin C in liver cells, which were very low in the aged rats, was restored to the level seen in young rats when they were given alpha lipoic acid and acetyl-L-carnitine.[70]

Photoageing of the facial skin has shown improvement with topical applications of alpha lipoic acid. In one study, 33 women with a mean age of 54.4 years, half of the face was treated twice a day for 12 weeks with cream containing 5% alpha lipoic acid and the other half with the control cream. The methods used to assess the improvement were self-evaluation by the women, clinical evaluation, photographic evaluation, and laser profilometry. All four methods of assessment showed a significant improvement on the side of the face treated with the cream containing alpha lipoic acid compared to the placebo-treated half of the face. [71]

Alpha lipoic acid has been used to improve mental function and might be a successful therapy for Alzheimer's disease and other related dementias. Mitochondria are known to lose efficiency with age due to the oxidation of proteins, lipids, DNA, and RNA.[72] Age-related decay of mitochondrial function can be partially reversed in older animals by treatment with dihydrolipoic acid. In one study, older rats receiving the reduced form of alpha lipoic acid showed signs of reduced lipid peroxidation and improved memory. Electron microscope studies in the

hippocampus region of the brain showed that the alpha lipoic acid reversed age-associated mitochondrial structural decay.[73] In a study with aged beagle dogs, a daily supplement of alpha lipoic acid and acetyl-L-carnitine for a period of 2 months significantly improved their learning ability on two landmark discrimination tasks compared to controls.[74]

Alpha lipoic acid has been shown to have a variety of properties which can interfere with pathogenic principles of Alzheimer's disease. For example, alpha lipoic acid increases acetyl-choline production by activation of choline acetyltransferase and increases glucose uptake, thus supplying more acetyl-CoA for the production of ACh. Alpha lipoic acid chelates redox-active transition metals, thus inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species, thereby increasing the levels of reduced glutathione. Via the same mechanisms, a decrease of inflammatory processes is also achieved. Alpha lipoic acid can scavenge lipid peroxidation products such as hydroxynonenal and acrolein. The reduced form of alpha lipoic acid, dihydrolipoic acid, is the active compound responsible for most of these beneficial effects.[75] In a study by German researchers, alpha lipoic acid was administered to 9 Alzheimer's patients for a year. The supplement led to a stabilization of cognitive functions as determined by constant scores in two neuropsychological tests.[76] And in a second study, researchers have shown that alpha lipoic acid protects cortical neurons from the toxic effects of two oxidative substances implicated in Alzheimer's disease.[77]

Parkinson's disease, a neurodegenerative disorder, may also be improved by alpha lipoic acid. In an animal model, the pathogenic mechanisms that lead to neurodegeneration were studied by administering a neurotoxin to mice. This toxin was shown to activate apoptosis signal regulating kinase (ASK1) and the phosphorylation of downstream kinases MKK4 and JNK. The administration of alpha lipoic acid with the neurotoxin abolished these effects and was able to afford neuroprotection.[78]

Other chronic diseases that alpha lipoic acid has shown to be of benefit for are some of the most common chronic disease conditions: metabolic syndrome, diabetes, and cardiovascular disease. Metabolic syndrome is characterized by a group of risk factors that include obesity, high LDL cholesterol and triglycerides, high blood pressure, and insulin resistance. These risk factors increase the risk of developing cardiovascular disease and diabetes. In animal experiments, alpha lipoic acid has been shown to cause weight loss, ameliorate insulin resistance and atherogenic dyslipidemia, as well as lower blood pressure.[79] Alpha lipoic acid has been shown to have anti-obesity effects. There is a fuel sensor in the cell called AMP-activatted protein kinase that is activated when cellular energy is depleted. Administration of alpha lipoic acid to rodents has caused a decrease in AMP-activated protein kinase activity, causing profound weight loss by reducing food intake and enhancing energy expenditure.[80]

In a recent randomized, double-blind clinical trial, endothelium-dependent vasodilation of the brachial artery was increased by 67%, 44%, and 75% in groups receiving irbesartan (an angiotensin-blocking drug), lipoic acid, and irbesartan plus lipoic acid, respectively, compared to placebo. Treatment with irbesartan and lipoic acid was also associated with significant reductions in plasma levels of pro-inflammatory mediators, such as interleukin-6.[81]

The most widely noted clinical application of alpha lipoic acid is in the treatment of diabetes and its complications. Acting as an antioxidant, R-dihydro-lipoic acid has been shown to protect rat pancreatic islet cells from destruction by reactive oxygen species.[82] Lester Packer, an antioxidant authority, notes that alpha lipoic acid works against insulin resistance by increasing the permeability of cell membranes, which is decreased and prevents the uptake of glucose.[83] High doses of alpha lipoic acid can improve glucose utilization in individuals with type 2 diabetes by increasing glucose uptake in skeletal muscles, as well as by enhancing insulin-stimulated glucose disposal.[84] [85] The increased burning of glucose may occur because alpha lipoic acid enhances glucose utilization by the mitochondria in the cells. In a small clinical trial, 13 patients with type 2 diabetes mellitus were given a single intravenous infusion of 1000 mg of alpha lipoic acid. The alpha lipoic acid improved insulin sensitivity by 50% compared to a placebo infusion.[86] Another study of 72 patients with type 2 diabetes found that oral administration of alpha lipoic acid at doses of 600 mg/day, 1200 mg/day, or 1800 mg/day improved insulin sensitivity by 25% after 4 weeks of treatment.[87] They found that there were not significant differences among the three doses of alpha lipoic acid, which indicated that 600 mg/day may be the maximum effective dose.[88] In a study of lean and obese patients with type 2 diabetes, treatment with 600 mg of alpha lipoic acid was found to prevent hyperglycemia-induced increments of serum lactate and pyruvate levels and increases glucose effectiveness.[89] R-alpha lipoic acid may be more effective in improving insulin sensitivity than S-alpha lipoic acid, according to studies with animals. One study found that R-alpha lipoic acid increased glucose uptake by skeletal muscle of obese rats by 65%, while S-alpha lipoic acid only increased glucose uptake by 29%.[90]

Alpha lipoic acid has been used extensively in Germany for the treatment of diabetic neuropathy, a type of nerve damage that causes pain, loss of sensation and weakness.[91] Both oral and intravenous alpha lipoic acid are approved for the treatment of diabetic neuropathy in Germany.[92] Three large-scale, double blind, placebo-controlled trials, called the Alpha-Lipoic Acid in Diabetic Neuropathy (ALADIN) studies, have looked at the neurological effects of alpha lipoic acid. The first ALADIN study found that alpha lipoic acid used for 3 weeks intravenously at 600 or 1,200 mg per day was superior to a placebo for reducing the symptoms of neuropathy. The 600 mg dose had slightly better results with fewer side effects.[93] The second ALADIN study examined nerve conduction parameters as well as Neuropathic Disability Score of 65 patients with type 1 or 2 diabetes. The trial lasted for 2 years, and patients were

divided into three groups: the first group received 600 milligrams of alpha lipoic acid twice a day, the second group received 600 milligrams of alpha lipoic once a day, and the third group received a placebo. The study found that alpha lipoic acid resulted in significant improvement in some of the nerve conduction parameters, but not in the Neuropathic Disability Score compared to the placebo group.[94] In the ALADIN III trial, 509 type 2 diabetics with peripheral neuropathy received either 600 milligrams of alpha lipoic acid intravenously for three weeks, followed by 600 milligrams orally three times daily for six months, or 600 milligrams of intravenous alpha lipoic acid for three weeks followed by a placebo for six months, or a double placebo. In the groups treated with alpha lipoic acid, there was a significant improvement in nerve function.[95] In another trial, known as the SYDNEY trial, 120 type 2 diabetics were given 600 milligrams of alpha lipoic acid intravenously or a placebo for five days a week for a total of 14 treatments. The group receiving the alpha lipoic acid reported significant improvement in overall symptoms compared to the placebo.[96] A meta-analysis of four placebo-controlled trials that have been done (ALADIN I and III, SYDNEY and an unpublished trial) found that the same treatment with 600 milligrams per day of intravenous alpha lipoic acid for 3 weeks in all trials significantly reduced the symptoms of diabetic neuropathy, and the analysis also found continuous daily improvement in symptom scores beginning on the eighth day of treatment.[97]

The oral form of alpha lipoic acid in the treatment of neuropathy is also beneficial, although studies show it may not be quite as useful as the intravenous form. In one trial, 24 type 2 diabetic patients were randomly assigned 600 milligrams of alpha lipoic acid three times a day or a placebo for three weeks. Significant improvement in symptoms of pain, burning, and numbness were reported in the group receiving the alpha lipoic acid.[98] In one of the longest controlled trials using oral alpha lipoic acid therapy, 299 diabetic patients with peripheral neuropathy were given either 1200 milligrams per day of alpha lipoic acid, 600 milligrams per day of alpha lipoic acid, or a placebo. The length of the study was 2 years and by that time only 65 of the original participants were included in the final analysis. Of those, the patients taking either amount of alpha lipoic acid showed significant improvement in electrophysiological tests of nerve conduction compared with those who took the placebo.[99]

Cardiac autonomic neuropathy is another neurological complication of diabetes. It occurs in as many as 25% of diabetic patients.[100] In a trial of 72 patients with type 2 diabetes, 800 milligrams per day of alpha lipoic acid resulted in a significant improvement in 2 out of 4 measures of heart rate variability when compared to a placebo.[101] And studies with mice have revealed that alpha lipoic acid may act as a protective agent for reducing cardiovascular complications of diabetes. Mice that were made diabetic and normal mice that served as controls were given a high fat/low cholesterol diet with or without alpha lipoic acid. At 20 weeks, the markers of oxidative stress were significantly lower in the mice receiving the alpha lipoic acid

compared to those without it. The increase in cholesterol, atherosclerotic lesions, and general deterioration of health caused by diabetes were completely prevented by alpha lipoic acid. There was also a reduction of blood glucose levels and the regeneration of insulin producing cells in the pancreas and cells in the pancreas were protected from damage.[102] Diabetics are also at high risk for vascular disease because endothelial function is often impaired in diabetic patients.[103] In a randomized controlled trial, 58 patients diagnosed with metabolic syndrome were given 300 milligrams per day of alpha lipoic acid orally for 4 weeks. Using ultrasound to measure flow-mediated vasodilation, those receiving alpha lipoic acid improved 44% compared to the placebo group.[104]

Delayed or impaired wound-healing is another complication of diabetics caused by the underlying factor of peripheral vascular dysfunction. Injuries often fail to heal because of high concentrations of pro-inflammatory cytokines present in the wound. Alpha lipoic acid has been shown to improve wound healing in studies with rats. In one study, diabetic rats were given alpha lipoic acid for 8 weeks. They were then subjected to abrasion wound formation. The wounds in the diabetic rats treated with alpha lipoic acid healed more rapidly than the wounds in the untreated diabetic rats.[105] These findings suggest that alpha lipoic acid might help to improve the healing of wounds in diabetics. In a study with humans undergoing hyperbaric oxygen therapy, alpha lipoic acid supplementation was able to accelerate wound repair in patients affected by chronic wounds. Alpha lipoic acid, in combination with hyperbaric oxygen therapy, down-regulate inflammatory cytokines and growth factors, promoting the healing process.[106]

Alpha lipoic acid has been found to be useful for multiple sclerosis. Reactive oxygen species, or free radicals, play an important role in many of the events underlying multiple sclerosis. Reactive oxygen species are known to effect the migration of monocytes and cause a dysfunction of the blood brain barrier. To infiltrate the central nervous system, monocytes must cross the blood brain barrier. They are then able to begin the process of demyelination and axonal damage. In a rat model for multiple sclerosis, acute experimental allergic encephalomyelitis, alpha lipoic acid prevented the development of the clinical signs of multiple sclerosis. Alpha lipoic acid inhibited the migratory capacity of the monocytes, and also stabilized the integrity of the blood brain barrier.[107] In one experiment with mice, feeding high doses of alpha lipoic acid was found to slow the progression of autoimmune encephalomyelitis, a model of multiple sclerosis.[108] The alpha lipoic acid inhibited the activity of an enzyme know as matrix metalloproteinase (MMP)-9 in these animals. When a small pilot study evaluated the safety of alpha lipoic acid in 30 people with relapsing of progressive multiple sclerosis, treatment with 1200-2400 milligrams per day of oral alpha lipoic acid showed that it was well-tolerated and that there were decreases in serum MMP-9 levels.[109]

Migraine headaches may be improved by treatment with alpha lipoic acid. In a study in Belgium, a randomized double-blind placebo-controlled trial of alpha lipoic acid was undertaken to see if alpha lipoic acid may be beneficial in migraine headache treatment. Five Belgian centers recruited 44 patients with migraine headaches. They received either a placebo or 600 milligrams of alpha lipoic acid per day for 3 months. Monthly migraine attacks were reduced during the treatment period in the alpha lipoic acid group compared to the placebo group. A within-group analyses showed a significant reduction of frequency of migraine attacks, migraine days, and migraine severity in the patients treated with alpha lipoic acid for 3 months. No adverse effects were reported and this study indicates that alpha lipoic acid may be a beneficial migraine prophylaxis.[110]

Alpha lipoic acid may be of benefit in cardiovascular disease. The risk factors of atherosclerosis, high cholesterol, smoking, diabetes mellitus, high homocysteine levels and hypertension, have one thing in common: the generation of oxidative stress.[111] Oxidative influences on LDL cholesterol causes an increase in the atherogenicity by altering cell receptor uptake of these particles.[112] The oxidized LDL is taken up by scavenger receptors on monocytes, smooth muscle cells and macrophages in a process leading to the accumulation of lipids and the formation of foam cells, an early feature of atherosclerotic plaques. Inflammatory events then occur within the newly formed lesion that further generate peroxides, superperoxides and hydroxyl radicals within the endothelium, causing a cycle that further damages the vasculature. Because of it's ability to recycle antioxidants, alpha lipoic acid may protect against free radical LDL cholesterol oxidation and decrease the risk of cardiovascular disease. [113] In a study that was done with quail, alpha lipoic acid was shown to have a protective effect on the buildup of plaque in the arteries, a characteristic of atherosclerosis. The group receiving the alpha lipoic acid had 75% fewer atherogenic lesions than the control group. The researchers suggested that the alpha lipoic acid may guard against atherosclerosis by preventing oxidation of LDL cholesterol and/or by recycling vitamin E.[114] Another study found that dietary alpha lipoic acid of 1 milligram per kilogram of diet reduced the levels of total cholesterol and lipoproteins in the serum and aortic tissue of rabbits. [115] In a more recent study, researchers found that supplementing mice with lipoic acid reduced arterial lesion formation, triglycerides, blood vessel inflammation and weight gain, all of which are factors involved in the development of cardiovascular disease. They used apolipoprotein E-deficient and apolipoprotein E/low-density lipoprotein receptor-deficient mice, which are established models of human heart disease. The mice were divided to receive diets containing a normal amount of fat or extra fat, with or without supplemental lipoic acid, for ten weeks. The amount of alpha lipoic acid was the human equivalent to 2 grams per day. The mice receiving the supplement had a significant reduction of atherosclerotic lesion formation in both groups eating varying amounts of fat. Supplemented mice also had 40 percent less weight gain and lower triglycerides in both serum and very low-density lipoprotein compared to those that did not receive the supple

ment. Less inflammation was also experienced in the supplemented mice.[116] Researchers from Beijing University found that alpha lipoic acid, because of its free-radical scavenging effects, is able to protect the myocardium from free-radical damage and decrease the incidence of malignant arrhythmias.[117]

Hypertension may be improved with alpha lipoic acid. In hypertensive patients, lower concentrations of antioxidants and superoxide dismutase activity have been documented.[118] In one study, rats were given a diet supplemented with alpha lipoic acid for 9 weeks. After 9 weeks, results showed lowered systolic blood pressure, cytosolic [Ca2+]i, blood glucose and insulin levels, and tissue aldehyde conjugates.[119] In another study, rats were given 10% D-glucose in their drinking water combined with either a normal chow diet or with an alpha-lipoic supplemented diet, and they were compared with control rats during 3 weeks. The rats fed chronic glucose developed non-insulin dependant diabetes as reflected by an increase in both blood glucose and insulin levels. They also had a progressive increase in systolic blood pressure, an increased level of superoxide anion, and a lower plasma glutathione peroxidase activity level. However, supplementation of alpha lipoic acid in the diet of glucose fed rats prevented the rise in blood pressure, the increase in superoxide production, the decrease in plasma glutathione peroxidase, and the development of insulin resistance. This study suggests that the antihypertensive and hypoglycemic effects of alpha lipoic acid are associated with the oxidative stress as reflected by the decrease in the basal superoxide anion production and by the preservation of the activity of glutathione peroxidase in the plasma of chronically glucose-treated rats.[120]

AMP-activated protein kinase (AMPK) acts as a fuel sensor in the cell and is activated when the energy in the cell is depleted. AMPK is important in the regulation of food intake and energy expenditure in the body. Alpha lipoic acid has been shown to decrease hypothalamic AMPK activity and cause profound weight loss in rodents by reducing food intake and improving energy metabolism. Through this mechanism, alpha lipoic acid exerts anti-obesity effects.[121] Alpha lipoic acid is also able to enhance fatty acid oxidation and reduce lipid accumulation due to activating AMPK in skeletal muscle. In a study with rats, alpha lipoic acid was able to lower triglyceride accumulation in the skeletal muscle of obese rats and increase insulin-stimulated glucose disposal.[122] Obesity has been found to be associated with increased cardiovascular mortality.[123] Endothelium-dependant vascular relaxation is impaired in obese rats and this impairment has been found to be associated with increased lipid accumulation and decreased AMPK acitivities in endothelial cells.[124] This has also been seen to be an early event in the development of atherosclerosis.[125] In a study using obese rats, alpha lipoic acid was found to reduce food intake, normalize body weight, and normalize metabolic parameters, such as triglycerides and insulin. Alpha lipoic acid was found to improve vascular dysfunction and normalize AMPK activities in the endothelial cells.[126]

Alpha lipoic acid may also be beneficial during an acute stroke. It is able to inhibit platelet and leukocyte activation and adhesion, reduce free-radical generation, and increase cerebral blood flow. Ischemia is the condition suffered by tissues & organs when deprived of blood flow. It is due mostly to the effects of inadequate nutrients and oxygen. Reperfusion injury refers to the tissue damage inflicted when blood flow is restored after an ischemic period of more than about ten minutes. Ischemic-reperfusion injury in humans occurs in conditions such as stroke, cardiac arrest, subarachnoid hemorrhage or head trauma. Tissue damage is observed during reperfusion, which is primarily attributed to oxidative injury resulting from production of oxygen free radicals. Several animal studies have shown that dihydrolipoic acid, not alpha lipoic acid, has demonstrated a protective effect against ischemia reperfusion injury in the brain.[127] [128] However, in a gerbil animal study, it was the synthetic form of alpha lipoic acid that was found to protect against ischemia reperfusion injury. When animals were treated with alpha lipoic acid for seven days prior to the ischemia reperfusion injury, they had less change in locomotor activity and less damage to brain cells than the control animals. [129] And in another study with rats, pretreatment with alpha lipoic acid before brain ischemia reduced mortality from 78% to 26% in the 24 hour period following the reperfusion. This pretreatment with alpha lipoic acid protected the brain from the loss of glutathione normally caused by ischemia reperfusion injury and significantly reduced the elevation in lipid peroxidation.[130] In another study in which hearts from rats fed alpha lipoic acid were anaylized, the alpha lipoic acid was found to preserve vitamin E in the heart tissue, to decrease lipid peroxidation, and improved the recovery of the function of the left ventricle.[131] When alpha lipoic acid was studied on strokes induced in mice, administering a subcutaneous injection 1.5 hours before the stroke was induced was shown to reduce the infarct volume in middle cerebral artery occlusion. Treatment with alpha lipoic acid produced a significant reduction in lesion size at 24 hours and a significant improvement in neurological function at 24 hours. This study shows that taking alpha lipoic acid before the onset of a stroke can prevent some of the neurological damage caused by the stroke. In this study, the mechanism of action of alpha lipoic acid appears to be due to its ability to substitute for glutathione. Free radical injury causes a depletion of cellular glutathione, leading to oxidation of protein thiols to disulfides and the loss of enzymes having thiol groups.[132]

Alpha lipoic acid has been shown in animal models to have a beneficial effect on heavy metal poisoning. Heavy metals, particularly cadmium, arsenic, and mercury, cause cellular damage by harming the mitochondria, inhibiting mitochondrial enzymes, suppressing protein synthesis, and producing free radicals.[133] In one study, dogs and mice were completely protected from arsenite poisoning and mercury poisoning with high doses of alpha lipoic acid, but it was ineffective against lead and gold poisoning.[134] Alpha lipoic acid can form a complex with arsenic that renders that arsenic nontoxic.[135] In studies using mice, alpha lipoic acid has shown to prevent intestinal uptake of arsenic and reduce the toxic effect of arsenic on enzyme

inhibition.[136] Alpha lipoic acid has been shown to protect rat hepatocytes from cadmium toxicity at concentrations of 5 mM. It decreased cadmium uptake by the hepatocytes and normalized glutathione levels, increasing survival and cell viability despite cadmium toxicity. [137] In another study using rats, treatment with alpha lipoic acid completely prevented cadmium-induced lipid peroxidation of the heart, brain, and testes. Glutathione concentrations in the brain were 63% decreased in the rats treated with cadmium, but only 4% increased in rats treated with both cadmium and alpha lipoic acid.[138] Alpha lipoic acid can protect the cells from lipid peroxidation caused by excess copper. It has been shown to bind copper in human lipoproteins and to inhibit peroxidation of the lipoproteins.[139] Wilson's disease has been successfully treated with alpha lipoic acid due to its ability to increase renal copper excretion and to normalize liver function.[140]

High levels of iron, particularly in the brain, along with an increased level of unsaturated fatty acids lead to increased levels of tissue peroxidation. The free radicals that are formed by reactions with iron in the central nervous system have been found to be suppressed by alpha lipoic acid.[141] The heavy metal, platinum, can cause renal toxicity. In experiments with rats with cisplatin-induced renal damage, large doses of alpha lipoic acid were able to restore the antioxidant enzyme activity levels to normal, increase glutathione levels, and decrease renal platinum content.[142] Lead toxicity has also been shown to be improved in animal models. In one study, an intraperitoneal injection of 25 milligrams of alpha lipoic acid was given to rats for seven days. It increased glutathione levels 207% and decreased malondialdehyde levels in the brain, kidneys, and red blood cells.[143]

Another use for alpha lipoic acid is for burning mouth syndrome and idiopathic dysgeusia, an altered perception of taste. In one study, 22 patients with idiopathic dysgeusia were given alpha lipoic acid for 2 months. The results showed significant symptom improvement compared to the placebo group.[144] Another study looked at the effect of alpha lipoic acid on burning mouth syndrome. Forty two patients with burning mouth syndrome were divided into 2 groups. One group was given 600 milligrams of alpha lipoic acid for 20 days, followed by 200 milligrams for 10 days. The control group was given a placebo for 30 days. Results showed significant improvement in two thirds of the people receiving alpha lipoic acid, while only 15% of those taking the placebo had improvement. When those who had taken the placebo were switched to alpha lipoic acid, up to two thirds showed significant improvement as well.[145]

As people age, they tend to produce excess levels of inflammatory cytokines such as interleukin-6, interleukin-1b, and tumor necrosis factor alpha (TNF-alpha). Cytokines are immune system-regulating chemicals. Pro-inflammatory cytokines can induce a state of chronic inflammation and can damage the bone matrix of the body. Studies have shown that alpha lipoic

acid can inhibit the damage to human bone marrow cells caused by TNF-alpha. In one study, TNF-alpha caused an increase in intracellular reactive oxygen species and reduced cellular glutathione levels, leading to cell death. When the cells were pretreated with alpha lipoic acid, these changes induced by TNF-alpha were prevented. Alpha lipoic acid may have a therapeutic role in stopping bone loss associated with oxidative stress.[146] Another study found alpha lipoic acid to inhibit osteoclast differentiation by reducing NFK-kappaB DNA binding and it also was found to prevent bone loss.[147]

Alpha lipoic acid may also play an important role in improving hearing loss. In a study with aging rats, alpha lipoic acid was found to improve cochlear function by improving mitochondrial function.[148] Damage to the ear is a side effect of many drugs and alpha lipoic acid may provide protection from these side effects. A study examined the use of alpha lipoic acid for hearing loss associated with cisplatin, a widely used anticancer drug. Cisplatin's clinical use is limited by the onset of severe side effects, one of them being toxicity to the ear and deafness. Evidence suggests that free radicals are involved in the ototoxic effects of cisplatin and that the use of cisplatin results in depletion of glutathione and antioxidant enzymes (superoxide dismutase, catalase, glutathione-peroxidase and glutathione-reductase) in cochlear tissues, with a corresponding increase of the malondialdehyde levels.[149] Studies have also shown that alpha lipoic acid lessens nerve damage induced by aminoglycoside antibiotics. In experiments carried out with guinea pigs, alpha lipoic acid was found to reduce cochlear damage that the drug amikacin caused in the control group.[150] Exposure to high energy impulse noise caused by explosions can result in damage to the auditory system. Rats were used for a study which examined whether a short period of pre-exposure supplementation with antioxidants would protect the ear from the effects of noise. The rats given alpha lipoic acid for three days before being exposed to noise showed a much higher measurement of blood oxygenation than the controls. The alpha lipoic acid was able to protect the ear from free radical stress, antioxidant depletion, and hemoglobin oxidation that occurs after the exposure to high energy impulse noise.[151]

Adriamycin, an anthracycline antibiotic, which is widely used as an anticancer drug in the treatment of various solid tumors, has been shown to induce reproductive abnormalities in males. In a study with rats, the effect of alpha lipoic acid was investigated on adriamycin-induced testicular toxicity. Adriamycin caused a significant increase in DNA damage in the sperm, a significant decrease in the activities of steroidogenic enzymes, and decreased serum testosterone levels. However, treatment with alpha lipoic acid one day prior to adriamycin administration was able to maintain near normal steroidogeneis and spermatogenesis, thereby proving it to be an effective cell protectant.[152] Adriamycin also causes a significant decrease in the activities of mitochondrial antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and glutathione reductase, in the testis. But pre-treatment with alpha

lipoic acid before exposure to adriamycin resulted in the ability to maintain near normal activities of the enzymes in the mitochondria in an experiment with rats.[153] The oxidative stress caused by adriamycin also causes damage to the red blood cells, resulting in lowered hemoglobin and hemacrit levels, and increased lipid peroxidation of the cell membrane. But when rats were given alpha lipoic acid before they were given the adriamycin, it was effective in counteracting the biochemical disturbances and toxic effects of the adriamycin.[154]

Alpha lipoic acid is able to exert a protective effect on the liver when it is exposed to poisons and toxins. One study examined the protective effects alpha lipoic acid has on liver and kidney toxicity in rats that were given an oral toxic dose of acetaminophen. The rats were pretreated with 100 milligrams per kilogram of alpha lipoic acid and then given an oral toxic dose of acetaminophen. None of the animals pretreated with alpha lipoic acid died, and the elevation of nitric oxide production, reduction of glutathione peroxidase, and depletion of intracellular reduced glutathione levels in the liver and kidneys, were suppressed by the alpha lipoic acid. This treatment completely prevented acetaminophen-induced mortality and inhibited oxidative stress in the liver and kidneys.[155] [195] Another study looked at the action of alpha lipoic acid on the antioxidant system in rats with toxic hepatitis. Injections of alpha lipoic acid caused a decrease in the levels of glutathione reductase and peroxidase to normal levels. It was shown to regulate the manifestations of oxidative stress and the state of the glutathione antioxidant system.[156] A German study found alpha lipoic acid beneficial in the treatment of chronic liver diseases. When 89 patients with liver diseases (42 with chronic hepatitis, 25 with hepatic cirrhosis, 14 with hepatitis, and 8 with adiposis hepatica) were given oral and intravenous alpha lipoic acid, good results were achieved.[157]

Researchers examined the protective effects of alpha lipoic acid on the oxidative damage caused by acrolein, a major toxicant in cigarette smoke, in human retinal pigment epithelial cells. Smoking is a cause of severe oxidative stress and has been shown to deplete ascorbic acid levels and cause oxidation of lipids and proteins.[158] [159] Three large studies have found a link between smoking and age-associated macular degeneration.[160] Of the six main toxic chemicals in cigarette smoke, acrolein has one of the highest hazard indexes and is much more toxic than formaldehyde and acetaldehyde, and can reach 80 μM in the respiratory tract fluid in smokers.[161] Acute exposure to acrolein in the retinal cells caused decreases in cell viability, mitochondrial potential, glutathione levels, antioxidant capacity, Nrf2 expression, and enzyme activity. Cells lost 79% and 87% of viability after ARPE-19 cells were exposed to 50 and 100 μM acrolein for 24 hours, whereas lower concentrations (1–25 μM) of acrolein had no apparent effect. When the cells were pretreated with alpha lipoic acid, the cells were protected from the oxidative damage caused by acrolein exposure. Alpha lipoic acid was able to maintain the intracellular antioxidant levels, glutathione levels, and protect against mitochondrial damage. It has been estimated that the acrolein level that is in cigarette smoke is

approximately 25 to 140 µg per cigarette.[162] Because smoking is a habitual activity and the concentration of acrolein during smoking is less than that shown in the acute exposure seen in this study, the researchers also exposed the retinal cells to low doses of acrolein for 8 days or 32 days. They found that long term exposure caused similar toxicity in the cells.[163]

Alpha lipoic acid has a remarkable effect on the liver. American physician, Dr. Burton Berkson, was one of the first doctors to conduct large human clinical studies on alpha lipoic acid. In the 1970's, he worked with Dr. Fredrick C. Bartter and other associates from the National Institutes of Health investigating the use of alpha lipoic acid on liver damage. They administered alpha lipoic acid to 79 people with severe and acute liver damage at various hospitals around the United States, and 75 people recovered full liver function. He has since treated hundreds of patients with alpha lipoic acid for liver damage, autoimmune disease, cancer, and other diseases. His research and studies using alpha lipoic acid for hepatitis C have shown that it may be a low cost and efficacious alternative treatment program in combination with 2 other antioxidants. In Dr. Berkson's study, 3 patients with cirrhosis, portal hypertension and esophageal varices, secondary to a chronic hepatitis C infection, were given alpha lipoic acid, silymarin, and selenium. All 3 patients recovered quickly and their laboratory values improved markedly. They were able to avoid liver transplants and were able to resume normal lives. A closer look at his program with 3 patients will show that alpha lipoic acid is highly beneficial to the health of the liver.

In modern medicine, there is no reliable therapy for chronic hepatitis C infection since interferon and antivirals work no more than 30% of the time. Liver transplantation is another option, but is not always successful due to the residual viruses infecting the new liver. It is also extremely costly and can be a very painful and debilitating procedure. Dr. Berkson used the triple antioxidant combination of alpha lipoic acid, silymarin, and selenium in the treatment of 3 patients with chronic hepatitis C. These substances were chosen because of their ability to protect the liver from free radical damage, to increase the levels of other antioxidants in the body, and to interfere with viral proliferation. Each patient was given 600 milligrams of alpha lipoic acid, 900 milligrams of silymarin, and 400 micrograms of selenium per day. The patients were also prescribed B vitamins, vitamin C, vitamin E, and a mineral supplement. Dietary modifications that were suggested to the patients were to eat a diet that included at least 6 servings of vegetables and fruits, only 4 ounces or less of meat per meal, and 8 glasses of water per day. The patients were also instructed to reduce their stress levels and to take part in an exercise program.

The first patient, Mrs. M.P., is a 57-year-old woman who contracted hepatitis C after a blood transfusion during surgery 10 years ago. She did not have a healthy lifestyle at the time and did not eat a nutritious diet. She became very fatigued and nauseous about 5 years ago and

was diagnosed with non-A, non-B hepatitis. After treatment with conventional therapies, she continued to degenerate into a poorer state of health. She was diagnosed with chronic hepatitis C, cirrhosis, portal hypertension, esophageal varcies, and thrombocytopenis 3 years ago. The treatment with steroids and interferon did not improve her condition. Mrs. M.P. was told there was a mass in her liver that was probably cancer. When she came to Dr. Berkson's office, she was fatigued, weak, pale, and her abdomen was enlarged. She was given alpha lipoic acid, silymarin, and selenium, along with the other nutrients. Her lab work began to show favorable changes, and she was able to recover her health and became free of the signs and symptoms of a serious chronic hepatitis C infection.

The second patient, Mrs. P.P., is a 49-year-old woman who was infected with hepatitis C more than 10 years ago following a blood transfusion before trauma surgery. A liver biopsy was taken about 3 years ago that showed moderate cirrhosis with active inflammation. She also developed portal hypertension with esophageal varices. She was treated with interferon therapy, but did not receive any results. A liver transplant was her only option and her health continued to deteriorate. She came to Dr. Berkson's office with symptoms of fatigue, anxiety, and insomnia. Mrs. P.P. was given 600 milligrams of alpha lipoic acid, 900 milligrams of silymarin, and 400 micrograms of selenium, along with aprazolam for the insomnia. She improved her diet and lifestyle and in 7 months regained her health. She is working a full time job and plays sports without fatigue or any other of her previous symptoms.

The third patient, Mrs. L.M., is a 35-year-old mother of 3 children. She developed hepatitis because of a blood transfusion she was given during the birth of her child 15 years ago. When she became ill three years ago, she was diagnosed with cirrhosis of the liver, portal hypertension, and esophageal varcies. She also developed splenomegaly and thrombocytopenia as a result of her portal hypertension. It was recommened to Mrs. L.M. that she needed to get an evaluation for a liver transplant. When she came to Dr. Berkson's office, she complained of constant pain in the area of her liver and spleen. She was given the combination of alpha lipoic acid and other antioxidants. She began to feel much better within 2 weeks and recovered quickly. The pain in her liver ended and her energy level improved. She was able to return to her normal work as a housewife and returned to college the next semester earning a 3.8 grade point average.[164]

Alpha lipoic acid has been shown to have a protective effect against acute hepatitis due to copper toxicity in experiments with rats. The Long-Evans Cinnamon rats accumulate excess copper in their liver due to a genetic defect. It causes them to develop acute hepatitis with severe jaundice in a manner similar to patients with Wilson's disease. Alpha lipoic acid was administered to the rats by gavage in doses of 10, 30, and 100 milligrams per kilogram of body weight five times per week. Alpha lipoic acid prevented the loss of body weight and the

development of severe jaundice in a dose-dependant manner. Analysis of the antioxidant systems in the liver showed that alpha lipoic acid significantly suppressed the inactivations of catalase and glutathione peroxidase. It completely suppressed the increase in lipid peroxidation and was found to exert antioxidant effects at the molecular level.[165]

The protective effect of alpha lipoic acid on the liver has been studied in rats that suffered acute organ injuries. The rats were given a lipopolysaccaride to induce liver damage. The damage to the liver resulted in an increase in plasma alanine and aspartate aminotransferase activities and increases in tumor necrosis factor-alpha and nitric oxide concentrations. There was also increased hepatic myeloperoxidase activity, increased lipid peroxidation, and increased levels of other markers that showed an activation of the inflammatory response. When the rats were pretreated with alpha lipoic acid prior to the liver injury, there was a general reversal of the altered biochemical indices and a significant alleviation of liver injuries.[166]

There has been research on the treatment of human immunodeficiency virus (HIV) with alpha lipoic acid. Acquired immune deficiency syndrome (AIDS) is characterized by HIV infection and progressive depletion of T-cells and an impaired immune response. It is now widely accepted that one of the central features of HIV disease involves oxidative stress, which leads to cell death and a depletion of CD4 cells, or T-helper cells.[167] It has been demonstrated that the blood and tissues of HIV-infected individuals have increased oxidation reactions,[168] a deficiency of glutathione,[169] and increased amounts of free radicals.[170] Glutathione is necessary for regulating immune system T-cell activation and phagocytosis.[171] Alpha lipoic acid has the ability to raise glutathione levels as much as 30-70% both *in vivo* and *in vitro*, making it beneficial for HIV patients.[172] Raising glutathione levels has also been shown to alter the cytokine balance in favor of a Th1 immune response mode, an anticancer and antiviral mode of the immune system.[173] Patients with HIV have a compromised antioxidant defense system. Antioxidant levels in the blood are decreased and the peroxidation of lipids and proteins are typically increased in patients. In a pilot study, the short term effect of alpha lipoic acid on blood antioxidant levels and peroxidation products was investigated in HIV positive patients. In the majority of patients, alpha lipoic acid increased the plasma vitamin C levels, total glutathione levels, total blood thiol groups, and T helper lymphocyte levels, and decreased the lipid peroxidation products. The results of this study show that alpha lipoic acid changes the blood redox state of HIV infected individuals.[174]

Alpha lipoic acid has been found to be an effective inhibitor of HIV-1 virus replication. In cultured lymphoid T-cells, alpha lipoic acid was able to inhibit replication of the HIV virus and caused a 90% reduction in reverse transcriptase activity.[175] Nuclear factor-kappaB (NF-kappaB) is one of the cellular transcription factors involved in gene expression of the human

immunodeficiency virus. A randomized, double blind, placebo-controlled trial was done with 33 HIV-infected patients with a history of unresponsiveness to highly active antiretroviral treatment. They were given 900 milligrams of alpha lipoic acid per day or a placebo for 6 months. The glutathione level in the blood was significantly elevated after 6 months in the alpha lipoic acid-supplemented patients compared to insignificant change in the patients taking the placebo. The lymphocyte proliferation response was significantly enhanced in the patients receiving alpha lipoic acid compared to the group taking a placebo. Alpha lipoic acid was found to have a positive impact on patients with HIV by restoring blood glutathione levels and improving the reactivity of lymphocytes to T-cell mitogens.[176]

Alpha lipoic acid may also benefit arthritis. In a study with mice, alpha lipoic acid was found to suppress the development of collagen-induced arthritis and to protect against bone destruction. The mice were divided into 3 groups and were given 10 milligrams per kilogram of body weight of alpha lipoic acid, 100 milligrams per kilogram of body weight, or a placebo. The alpha lipoic acid treated mice had a dose-dependant reduction of the collagen-induced arthritis. It also prevented bone erosion and destructive changes. Intracellular reactive oxygen species in lymphocytes obtained from inguinal lymph nodes was significantly reduced in the mice given alpha lipoic acid. TNF-alpha, IL-1beta, and IL-6, which are pro-inflammatory cytokines, were reduced by the treatment with alpha lipoic acid. The alpha lipoic acid was able to improve the arthritis in the mice by the reduction of oxidative stress and the inhibiting of inflammatory cytokine activity.[177]

Because of its role as an antioxidant, alpha lipoic acid has been found to improve antibody response in immunosuppressed animals.[178] Alpha lipoic acid has been shown to cause cell death in some tumor cell lines.[179] Due to its ability to scavenge reactive oxygen species, alpha lipoic acid has been found to induce apoptosis, or cell death, in liver tumor cells. The apoptosis was dependant on the activation of the caspase cascade and the mitochondrial death pathway. Alpha lipoic acid was able to increase caspase-9 and caspase-3 activity. [180] In a study using human cancer cells, alpha lipoic acid was found to activate an enzyme that kills leukemia cells. Leukemic Jurkat cells were treated with 100 microM of alpha lipoic acid for 72 hours. The enzyme that plays an important role in initiating cell death was increased 100% with alpha lipoic acid.[181] Alpha lipoic acid was found to induce apoptosis in human colon cancer cells in another study. Alpha lipoic acid was found to increase caspase-3-like activity and increase the production of oxygen inside the mitochondria.[182] Another study examined the effect of alpha lipoic acid on liver cancer cells. Two different hepatoma cell lines were used, FaO and HepG2. Alpha lipoic acid was shown to inhibit the growth of both cell lines as indicated by the reduction in the number of cells, the reduced expression of cyclin A, and the increased levels of the cyclin/CDKs inhibitors. This study showed that alpha lipoic acid induces apoptosis in liver cancer cells, and suggests that it may be useful in liver cancer therapy.[183]

Alpha lipoic acid has been found to positively affect the long-term survival of a patient with pancreatic cancer that had metastasized to his liver. Following his diagnosis, he began a 21 day course of chemotherapy. Due to his poor tolerance for the chemotherapy, he decided to seek another opinion from a well-respected oncology center where he was told that there was little hope for his survival. When he came to Dr. Berkson's clinic, his quality of life was poor. He was losing weight and experiencing constant abdominal pain and nausea. He was put on intravenous alpha lipoic acid, 300-600 milligrams 2 days per week, and low-dose naltrexone, 4.5 milligrams at bedtime. In addition, he was given an antioxidant regime of 600 milligrams oral alpha lipoic acid, 400 micrograms of selenium, and 300 milligrams 4 times a day of silymarin to reduce the products of oxidative stress that was due to his disorder. After the first intravenous administration of alpha lipoic acid, the patient commented that he had an increase of energy and a sense of well-being. His quality of life began to improve tremendously after starting the treatment. He went back to work soon after starting this therapy and remains free of symptoms 3 years later. There were no toxic adverse effects from the treatment and his malignancy has not progressed several years after the treatment.[184]

Alpha lipoic acid may also be a valuable adjunct to chemotherapy. Studies with animals have shown that alpha lipoic acid is able to reduce the side effects associated with the chemotherapy drugs, cyclophosphamide and vincristine, but did not hamper drug effectiveness. [185] Alpha lipoic acid has been shown to synergistically improve the cytotoxicity of vitamin C against cancer cells in tissue culture. [186] In another study using human tumor cell lines, alpha lipoic acid was shown to induce hyperacetylation of histones in vivo and shown to have a differential effect on the growth and viability of normal versus transformed cell lines. This study showed that human cancer cell lines became apoptotic after being exposed to alpha lipoic acid and that alpha lipoic acid did not cause apoptosis in normal cells.[187]

Dihydro-lipoic acid has been found to inhibit skin tumor generation through its anti-inflammatory and antioxidant properties. Mice were given a topical application of 12-O-tetradecanoylphorbol on their skin. Dihydro-lipoic acid significantly inhibited the stages of inflammation and inhibited tumor formation.[188]

In a study with mice, alpha lipoic acid was investigated on a key inflammatory pathway and cell proliferation in cancerous ovarian epithelial cells. It was shown that alpha lipoic acid selectively inhibited the growth of the cancerous cells as compared to the non-cancerous cells of the ovary. The inhibitory effect was not due to apoptosis but instead is associated with an increase in the half-life of the cyclin-dependent kinase inhibitor, p27(kip1). The alpha lipoic acid also was found to inhibit TNF alpha-induced NF-kappa B signaling activity.[189] Rats with an aggressive cancer were treated with alpha lipoic acid in another study. The lifespan of the rats was increased by 25%.[190]

Lipoic acid has been found to improve the malignant character of bladder cancer cells through regulation of cellular β1-integrin localization. Ras proteins are oncogene products capable of inducing cell transformation and are associated with many types of human cancer. Frequency of mutation of *ras* family such as H-*ras*, K-*ras* and N-*ras* in human tumors is highly organ specific and H-*ras* mutation is common in bladder cancer. Alpha Lipoic acid inhibited the proliferation of T24 cells and inhibited cell migration and invasion of T24 cells, which were mimicked by extracellular signal-regulated kinase (ERK) and Akt pathway inhibition. Alpha lipoic also significantly downregulated the phosphorylated ERK and Akt levels and downregulated phosphorylated focal adhesion kinase level with disappearance of stress fiber formation. [191]

Alpha lipoic acid has been found to exert anti-proliferative effects on breast cancer. It downregulates the expression of the matrix metalloproteinase molecules and decreases their activity. By decreasing cellular migration and cellular motility, alpha lipoic acid provides decreased metastases. [192]

Another benefit of alpha lipoic acid was shown on gastric damage induced by indomethacin. The gastroprotective effects of alpha lipoic acid decreased the level of lipid peroxidation and the activities of myeloperoxidase and catalase in gastric tissues, and increased the level of glutathione and superoxide dismutase in the damaged stomach tissues. [193]

Adding to this already impressive array of favorable biological properties, new research has demonstrated in rats that the topical application of alpha lipoic acid produced an increase in skin wound healing. On the seventh day after surgery, animals treated with alpha lipoic acid showed increased healing rates versus control animals for the histological parameters analyzed. [194]

In conclusion, in vitro and in vivo studies suggest that alpha lipoic acid acts as a powerful nutrient with diverse pharmacologic and antioxidant properties. Pharmacologically, alpha lipoic acid is able to improve glycemic issues, neuropathies, and protect against toxicities associated with heavy metal poisoning. As an antioxidant, alpha lipoic acid has a direct effect on eliminating free radicals, chelates metal ions, increases glutathione and vitamin C levels. These diverse actions show how alpha lipoic acid can be effective in improving the pathology of many chronic diseases. Due to the fact that we are bombarded with more toxic chemicals than ever before in our daily environment, our bodies are exposed to an enormous amount of free radicals. The antioxidant protection that alpha lipoic provides may be one of the reasons that it confers so many health benefits and is useful for such a wide range of diseases.

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