

## ALPHA-LIPOIC ACID

**Description:** Also known as thiocetic acid or lipoic acid. Alpha-lipoic acid is a naturally occurring compound that is synthesized by plants and animals, including humans. It is a vitamin-like antioxidant containing two sulfur molecules (disulphide compound) that can be oxidized or reduced, and is easily absorbed through the gut and transported across cell membranes. Alpha-lipoic acid is sometimes referred to as a universal antioxidant, as well as the metabolic antioxidant. Because of the size and functionality of the molecule it is soluble in both water-based and fat-based areas of tissues. It is not as water-soluble as vitamin C, but it is much more water-soluble than vitamin E. This degree of water-solubility and fat-solubility will allow alpha-lipoic acid into all body systems. The main reason for this dual solubility is the size of the molecule. It is larger than ascorbic acid but it is much smaller than vitamin E.<sup>2</sup>

**Metabolism:** Alpha-lipoic acid is absorbed from the small intestine and distributed to the liver via the portal circulation and to various tissues in the body via the systemic circulation. Alpha-lipoic acid readily crosses the blood-brain barrier. It is found, after its distribution to the various body tissues, intracellular, intramitochondrially and extracellular. Alpha-lipoic acid is metabolized to its reduced form, dihydrolipoic acid (DHLA), by mitochondrial lipoamide dehydrogenase. DHLA, together with lipoic acid, form a redox couple.<sup>2</sup> Free alpha-lipoic acid is rapidly taken up by cells and reduced to DHLA intracellularly.

**Function:** As a disulphide compound, alpha-lipoic acid functions as a cofactor for several important enzymes, including energy metabolism reactions inside the mitochondria (Krebs cycle) as well as a potent antioxidant. DHLA functions directly as an antioxidant, while alpha-lipoic acid may have indirect antioxidant effects.<sup>3</sup> When large amounts of free alpha-lipoic acid are available as with supplementation (*see research Note*), alpha-lipoic acid is also able to function as an antioxidant.<sup>4</sup> When an antioxidant like vitamin C neutralizes a free radical, it becomes oxidized itself, and is not able to neutralize other free radicals until it has been reduced or regenerated. DHLA is a potent reducing agent, and has the capacity to regenerate a number of oxidized antioxidants to their active antioxidant forms. Specifically, DHLA is capable of reducing the oxidized forms of vitamin C, glutathione, and coenzyme Q<sub>10</sub>, which are able to regenerate oxidized alpha-tocopherol (vitamin E), forming an antioxidant network. DHLA can be regenerated from alpha-lipoic acid through the activity of enzymes present in cells.<sup>5</sup> Both DHLA and alpha-lipoic acid can act as a metal chelator, binding up excess copper, iron, mercury and cadmium, thus limiting the negative impacts of these heavy metals on the body.<sup>6, 7</sup> Glutathione is an important water-soluble antioxidant that is synthesized from the sulfur-containing amino acid cysteine. The availability of cysteine inside a cell determines its rate of glutathione synthesis. DHLA has been found to increase the uptake of cysteine by cells in culture, leading to increased glutathione synthesis.<sup>5</sup> There is evidence that alpha lipoic acid and DHLA have effects on regulatory proteins and on genes involved in normal cell growth and metabolism.<sup>8</sup> Several experimental and clinical studies have shown that, given the above attributes, alpha lipoic acid has potential therapeutic uses in preventing and/or treating such conditions as diabetes, atherosclerosis, cataracts, heavy metal poisoning, neurodegenerative diseases, and HIV infection.<sup>8</sup>

**Source:** Alpha-lipoic acid can be synthesized by plants and animals. It is unclear whether synthesis by normal gastrointestinal bacteria is a significant source of alpha-lipoic acid in humans. Biosynthesis does not appear to result in large amounts of circulating free alpha-lipoic acid, the form that is likely to function as an antioxidant.<sup>4</sup> Most alpha-lipoic acid in food is derived from lipoamide-containing enzymes and is bound to the amino acid, lysine (lipoyllysine). Animal tissues that are rich in lipoyllysine include kidney, heart, and liver, while plant sources that are rich in lipoyllysine include potatoes, spinach, broccoli, and tomatoes. Somewhat lower amounts of lipoyllysine have been measured in peas, brussels sprouts, and rice bran.<sup>9</sup>

**RDA:** No Recommended Daily Intake has been set. Nor has the issue been adequately studied. Some researchers believe that the amount needed for therapeutic antioxidant activity exceeds that produced by our bodies and consumed in a normal diet. As such, alpha lipoic acid is a strong candidate for

supplementation. Maintenance doses of 10-25 mg per day are suggested. Therapeutic doses of up to several hundred milligrams per day have been used.<sup>10</sup>

**Deficiency:** Lipoic acid deficiency has not been described, suggesting that humans are able to synthesize enough to meet their needs for enzyme cofactors. Increased destruction of the cofactor form of alpha-lipoic acid may underlie the pathology of some diseases. In arsenic toxicity, arsenic can form a complex with alpha-lipoic acid in dehydrogenase enzymes, leaving it inactive.<sup>4</sup>

**Safety:** There are no reports of toxicity from alpha-lipoic acid overdose in humans. Because controlled safety studies in pregnant and lactating women are not available, the use of alpha-lipoic acid supplements by pregnant or breastfeeding women is not recommended.<sup>11</sup>

**Drug Interaction:** Alpha-lipoic acid supplements may affect the optimal dose of medications used to control blood glucose in diabetics. Individuals on such hypoglycemic agents should monitor their blood glucose levels and consult their health care provider for dosage adjustments if necessary to prevent hypoglycaemia.<sup>11</sup>

**Nutrient Interaction:** Both alpha-lipoic acid and DHLA act to regenerate, and thus prolong the activity of, other antioxidant molecules including Vitamin C, glutathione, CoQ10, and, indirectly, Vitamin E.<sup>12</sup>

**Supplements:** Supplemental doses of alpha-lipoic acid are hundreds of times higher than the amounts that can be obtained from food, and should be considered pharmacologic. Alpha-lipoic acid is available by prescription in Germany, where it is approved for the treatment of diabetic and alcoholic neuropathies and alcoholic liver disease. It is available in the U.S. without a prescription as a dietary supplement.<sup>11</sup> Alpha-lipoic acid from supplements is rapidly absorbed, rapidly metabolized, and rapidly cleared from plasma and tissues, suggesting that it should be taken in divided doses throughout the day, rather than in a single daily dose.

**Stability:** At present, there are no studies showing the impact of cooking, storage, or processing on levels of lipoic acid in foods.

**Note:** Digestive enzymes do not break the bond between alpha-lipoic acid and lysine very effectively. Thus, it has been hypothesized that most dietary alpha-lipoic acid is absorbed as lipoyllysine, and free alpha-lipoic acid has not been detected in the circulation of humans who are not taking alpha-lipoic acid supplements.<sup>4</sup>

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