R-Lipoic Acid

Does your lipoic acid supplement contain only the form found in nature? Or does it also include a synthetic by-product that may interfere with the natural form's beneficial effects?

R-Lipoic Acid and R-Dihydrolipoic Acid (redox pair)

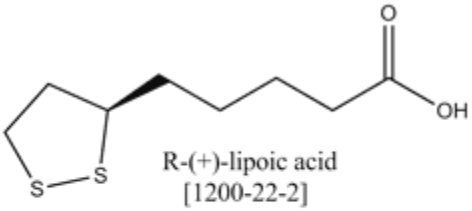
The only naturally occurring forms of alpha lipoic acid:

Alpha-Lipoic Acid Occurs In 3 Different Forms

When molecules are produced by industrial synthesis they exist in a "racemic form", which is a 50/50 composition of the two enantiomers. Enantiomers are mirror image molecules which are chemically unique.

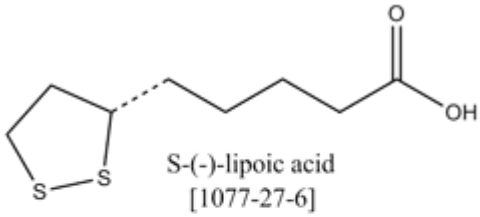
Alpha-lipoic acid consists of a 50/50 mixture of the R-(natural) and S-(unnatural) enantiomers and is called a 'racemic' mixture. It is the most widely available commercial form of lipoic acid.

There is evidence that the two enantiomers of alpha-lipoic acid have different biological activities.



R-(+)-lipoic acid
[1200-22-2]
$C_8H_{14}O_2S_2$
Mol. Wt.: 206.33
yellow crystals M.P.=46-48 deg C
with sintering
$[a]_{24.5}{}^{D}$ = +119 - +120 [c=1 in EtOH]

R-Lipoic Acid (the R (+) enantiomer) is the form of lipoic acid that occurs naturally in plants, animals and the body and is responsible for the specific beneficial effects of alpha lipoic acid. R-lipoic acid (RLA) is the only form that functions as a cofactor for mitochondrial enzymes. Of primary significance, R-lipoic acid has shown to be ten times more effective than racemic alpha lipoic acid for reducing inflammation.



S-(-)-lipoic acid
[1077-27-6]
$C_8H_{14}O_2S_2$
Mol. Wt.: 206.33
yellow crystals; M.P.=46-48 deg C
(with sintering)
$[a]_{24.5}{}^{D}$ = -119 - -120 [c=1 in EtOH]

S-Lipoic acid (The S (-) enantiomer) is not found in nature. S-Lipoic acid (SLA) is a by-product from chemical synthesis of racemic alpha-lipoic acid and may inhibit the most essential properties of the R form, including interactions with proteins, enzymes and genes.

Alpha-lipoic acid consists of 50/50 racemic mixture of the R and S enantiomers. Much of the research over the past 30 years has been done with racemic alpha lipoic acid because the R form was not commercially available. This was due to its instability and tendency to form polymerization products once isolated from the S form, and due to the challenges of delivering the R form to the body in bio-available dosage forms compared to racemic alpha-lipoic acid.

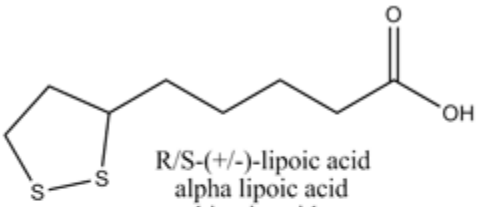
There is a clear indication of what the specific uses are claimed for the different enantiomers in the patent literature.

Functions in Health and Disease

R-Lipoic Acid (RLA) and its reduced form, R-Dihydrolipoic Acid (R-DHLA) may prove to be the most important nutraceutical compounds on the market today.

The redox couple has powerful antioxidant functions, serves as a critical co-factor in ATP production, regulates lipid and carbohydrate metabolism, signal transduction, gene transcription and cellular proliferation.

RLA/R-DHLA is neuroprotective, chelates heavy metals, can reverse enzyme and DNA oxidative damage and crosses the blood brain barrier. R-Lipoic Acid has been shown to be more effective by a factor of 8-10 over the commercially available alpha lipoic acid for reducing



R/S-(+/-)-lipoic acid
alpha lipoic acid
thioctic acid
rac-LA
[1077-27-6]
$C_8H_{14}O_2S_2$
Mol. Wt.: 206.33
yellow crystals; M.P.=58-61 deg C

inflammation, and with R-DHLA, regulates the pro-inflammatory COX-2 and LOX pathways. This indicates the unnatural SLA is interfering with the body's utilization of the R form.

R-Lipoic Acid (RLA) has superior activity in vivo

Some recent studies have suggested that the S-enantiomer has an inhibiting effect on the R-enantiomer, substantially reducing its biological activity and actually adding to oxidative stress rather than reducing it. Furthermore, the S-enantiomer has been found to reduce the expression of GLUT-4s in cells, responsible for glucose uptake, and hence reduce insulin sensitivity.

The superior activity of R-Lipoic Acid is due to stereospecific binding, whereas SLA competitively inhibits interactions at the redox-active sites of signaling proteins, transcription factorsa, histonesb and flavoenzymesc.

- Regulatory proteins that initiate the transcription of certain genes upon binding with DNA.
- Small proteins that are rich in basic amino acids and that bind to DNA, forming chromatin.
- Proteins that use a specific redox cycle to catalyze a variety of biological redox transformations.

The Benefits Of R-Lipoic Acid

- R-Lipoic Acid significantly reduces inflammation, an underlying cause of the degenerative diseases of aging and is more potent by a factor of 10 over commercial ALA.[1]
- R-Lipoic acid was found to reach higher plasma levels than S-lipoic acid when given orally as the racemic mixture in a human study.[2]
- R-Lipoic Acid protects body fats against oxidative damage and reverses stress damage in the heart.[3]
- R-Lipoic Acid was more effective than the S form in a battery of metal chelation tests. One hypothesis of the cause of diabetic complications involves overloading by transition metals which could explain the stereospecific effect of the R-form.[4]
- R-Lipoic Acid is the form of lipoic acid found in nature and therefore the form preferred by critical mitochondrial enzymes.[5, 6] A significant factor in aging is the decay of the mitochondria - and as we age, the efficiency of the mitochondria diminishes, as well as their quantity per cell.
- R-Lipoic acid is the only form of lipoic acid that was shown to expand total life span in immuno-suppressed mice.[7]
- R-Lipoic acid was much more effective than S-lipoic acid in enhancing insulin-stimulated glucose transport and metabolism in insulin-resistant rat skeletal muscle.[8]
- R-Lipoic acid was more effective than racemic alpha-lipoic acid and S -alpha-lipoic acid in preventing cataracts in rats.[9]
- R-Lipoic Acid increases cellular and mitochondrial antioxidant activity and prevents mitochondrial decay. This effectively attenuates the reported increase in oxidative stress with aging.[10]
- R-Lipoic Acid improves memory, reverses cognitive dysfunction, and protects the brain from neurodegeneration associated with aging.[10-12, 25]
- R-Lipoic Acid supplementation improves metabolic activity and lowers oxidative stress and damage evident in aging.[12, 13]
- R-Lipoic Acid significantly increase insulin sensitivity, enhances glucose transport, increases metabolic rate and reduces the gain in body fat from aging.[13, 14]
- R-Lipoic Acid has insulin-mimetic effects in glucose uptake in insulin resistant cells and may have therapeutic implications in restoring glucose availability in tissues such as the skeletal muscle.[15, 16]
- R-Lipoic Acid significantly increases or maintain levels of other antioxidants including Coenzyme Q10, vitamin C, vitamin E and glutathione.[16-18]
- R-Lipoic Acid prevents depletion of the glutathione pool within the cytoplasm and mitochondria. Pre-treatment of PC12 cells with R-Lipoic Acid leads to the preservation of mitochondrial complex I activity lost due to glutathione depletion.[18]
- R-Lipoic Acid increases the activity of the crucial mitochondrial PDH enzyme, important for nutrient metabolism (inhibited by age-related diseases such as diabetes) whereas SLA inhibits it.[19]
- R-Lipoic Acid , the natural enantiomer, is more effective than the S-(-) enantiomer at enhancing insulin-stimulated glucose transport and non-oxidative and oxidative glucose metabolism.[20]
- R-Lipoic Acid was reduced six to eight times more rapidly than S-lipoate in the rat heart.[21]
- R-lipoic acid prevented hyperglycemia, reduced insulin levels, and increased free radical scavenging potential.[22]
- R-Lipoic Acid, through its positive effects on cellular energy metabolism, attenuates metabolic dysfunction associated with advanced glycation endproducts (AGEs). AGEs accumulate on long-lived proteins, including beta-amyloid plaques in Alzheimer's disease and contributes to neuronal dysfunction and cell death.[23, 24]

- R-Lipoic Acid, a membrane permeable antioxidant, prevents the up-regulation of the AGE -induced gene expression responsible for regulating nitric oxide (NO) production. NO oxidizes and nitrates proteins which are markers of a chronic neuroinflammatory condition. This mechanism is relevant for Alzheimer's disease and for many chronic inflammatory conditions.[25]
- R-Lipoic Acid is the preferred substrate for the mitochondrial enzyme, dihydrolipoamide dehydrogenase, reacting 24 times faster than the S-enantiomer.[26]

Pro-oxidant Effects

It is now clear that many of the positive benefits and dangerous side effects of R-lipoic acid are the result of pro-oxidant effects. Since R-lipoic acid can interchange between a reduced form and an oxidized form, it displays reducing (antioxidant) and pro-oxidant properties related to dosage, 1/2 life and metabolism.

It is suggested that pro-oxidants produced by R-lipoic acid are involved in activation of insulin receptors and in elevated glucose uptake in muscle and fat cells. On the other hand, R-lipoic acid appears to protect the insulin-signaling cascade from oxidative stress-induced insulin resistance through its reducing capacities.

R-lipoic acid can effectively induce apoptosis in human colon cancer cells by a prooxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria.[28]

The ability of R-lipoic acid and/or R-Dihydrolipoic acid to function as either anti- or pro-oxidants, at least in part, is determined by the type of oxidative stress and the physiological circumstances.[27-30]

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