


**L-Theanine**

**DESCRIPTION**

L-theanine is a non-protein amino acid mainly found naturally in the green tea plant (*Camellia sinensis*). It is also found naturally in only one other known source, the edible mushroom *Boletus badius*, commonly known as the Bay bolete. L-theanine is the predominant amino acid in green tea and makes up 50% of the total free amino acids in the plant. The amino acid constitutes between 1% and 2% of the dry weight of green tea leaves. L-theanine is considered the main component responsible for the taste of green tea, which in Japanese is called umami. Umami, which was first described by a Japanese scientist over a hundred years ago, is now considered one of the five basic tastes: sweet, salty, sour, bitter and umami. Umami is the Japanese term for savory. L-theanine has been marketed in Japan for several years as a nutritional supplement for mood modulation and entered the United States dietary supplement marketplace a few years ago.

L-theanine is a derivative of L-glutamic acid. It is a water-soluble solid substance with the molecular formula C₇H₁₄O₃N and a molecular weight of 160.19 daltons. L-theanine is also known as gamma-ethylamino-L-glutamic acid, gamma-glutamylethylamide, r-glutamylethylamide, L-glutamic acid gamma-ethylamide and L-N-ethylglutamine. The chemical structure is:

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\begin{align*}
\text{H}_3\text{C} & \quad \text{NH}_2 \\
\text{HOOC} & \quad \text{C} & \quad \text{C} & \quad \text{N} & \quad \text{CH}_3 \\
\text{H}_2 & \quad & \text{H}_2 & \quad & & \\
\end{align*}
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**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

L-theanine may have activity in modulating the metabolism of cancer chemotherapeutic agents and ameliorating their side effects. It may also have mood-modulating activity and neuroprotective and immunoprotective effects.

**MECHANISM OF ACTION**

In animal tumor models, L-theanine has been found to increase the antitumor activity of some anthracycline agents (doxorubicin, idarubicin) and to ameliorate some of the side effects of these agents. It appears that L-theanine inhibits the efflux of these agents from tumor cells, increasing the inhibitory concentration of the drugs in the target cells. At the same time, L-theanine appears to decrease the oxidative stress caused by these agents on normal cells. Most of the side effects of these agents are due to oxidative stress. The mechanism by which L-theanine inhibits the efflux of such cancer chemotherapeutic agents as doxorubicin is unclear. L-theanine appears to have modest antioxidant activity, and this may explain, in part, L-theanine's ability to ameliorate some of the side effects of the chemotherapeutic agents. Further, L-theanine, by an unclear mechanism, appears to inhibit the influx of chemotherapeutic normal cells.

The mechanism of L-theanine's possible mood-modulating activity is also unclear. The amino acid might affect the metabolism and the release of some neurotransmitters in the brain, such as dopamine.

Human gamma-delta T cells are known to mediate innate immunity to microbes through T cell receptor-dependent recognition of unprocessed antigens with conserved molecular patterns. The nonpeptide alkylamine antigens are shared by bacteria fungi, parasites, tumor cells and edible plant substances, including mushrooms, apples and green tea. It has been shown that L-theanine, a precursor of the nonpeptide antigen ethylamine, primed peripheral blood gamma-delta T cells to mediate a memory response on reexposure to ethylamine and to secrete interferon (IFN)-gamma in response to bacteria. Such priming may enhance innate
immunity to bacteria and tumor cells and may account for some of the health benefits of green tea.

**PHARMACOKINETICS**

Little is known about the pharmacokinetics of L-theanine in humans. From animal studies, it appears that L-theanine is absorbed from the small intestine via a sodium-coupled active transport process and appears to cross the blood-brain barrier. It has been found in rat studies that the D-enantiomer of theanine may decrease the absorption of L-theanine, the L-enantiomer. It is unclear if D-theanine possesses any of the actions found with L-theanine. Not much is known beyond that. However, research is ongoing.

**INDICATIONS AND USAGE**

L-theanine has exhibited anticancer effects and an ability to favorably modulate the activity of some anticancer drugs in *in vitro* and animal experiments. It has also demonstrated hypotensive effects in animal work. It has increased LDL-cholesterol oxidation in preliminary *in vitro* tests. It was recently reported to enhance learning ability in animals and to induce relaxation in human subjects, possibly through its effects on serotonin, dopamine, and other neurotransmitters. It has also been shown to inhibit caffeine stimulation in another preliminary animal study. It demonstrates some neuroprotective and immunoprotective effects.

**RESEARCH SUMMARY**

L-theanine has been shown to enhance the anticancer activity of doxorubicin and idarubicin in *in vitro* and animal studies. In an *in vitro* study, L-theanine increased doxorubicin’s inhibition of Ehrlich ascites carcinoma more than two-fold and increased nearly three-fold the concentration of doxorubicin in the tumor compared with treatment with doxorubicin alone.

Subsequently, L-theanine, in combination with doxorubicin, was shown to significantly reduce tumor weight (to 62% of the control level) in M5076 ovarian sarcoma-bearing mice. The doxorubicin dose used in this combination was ineffective by itself in inhibiting tumor growth. L-theanine was reported to increase doxorubicin concentration in the tumor by two- to seven-fold while simultaneously decreasing doxorubicin concentrations in normal tissues.

A combination of L-theanine and doxorubicin significantly inhibited both primary ovarian sarcoma and hepatic metastasis of the tumor. L-theanine was credited in this study with enhancing the activity of doxorubicin.

In another study, L-theanine was used in conjunction with idarubicin, an anthracycline derivative used clinically to treat acute myelocytic leukemia. The use of idarubicin has been limited due to the frequency with which it produces severe leukopenia. Combined with idarubicin in the treatment of P388 leukemia-bearing mice, L-theanine significantly inhibited suppression of bone marrow cells and leukopenia, while simultaneously enhancing the antitumor activity of idarubicin.

L-theanine, in combination with doxorubicin, was further shown to have the ability to significantly inhibit even doxorubicin-resistant leukemia in mice.

In an *in vitro* test, L-theanine showed some ability to inhibit LDL peroxidation. The polyphenol component of a green-tea extract was more potent in this regard than the L-theanine component. The caffeine component, on the other hand, was less effective than L-theanine.

L-theanine has also exhibited hypotensive effects in spontaneously hypertensive rats but not in Wistar kyoto rats. Recently, L-theanine, at certain doses, was shown to inhibit caffeine stimulation, measured by electroencephalography in rats.

L-theanine, previously shown to penetrate the blood-brain barrier through the leucine-prefering transport system, has been demonstrated to produce significant increases in serotonin and/or dopamine concentrations in the brain, principally in the striatum, hypothalamus and hippocampus.

These findings led to recent studies investigating the possibility that L-theanine might enhance learning ability, induce relaxation and relieve emotional stress. Memory and learning ability were said to be improved in young male Wistar rats given 180 mg of L-theanine daily for four months. Performance was assessed using a test for learning ability and passive and active avoidance tests for memory.

In another recent study, rats fed L-theanine for three weeks *ad libitum* showed some signs of improved memory and learning. In a double-blind, randomized, placebo-controlled trial, the cognitive mood effects of L-theanine (250 mg) and caffeine (150 mg) were investigated both in isolation and in combination. The combination was found to improve some measures of mood and cognition. The mental effects of L-theanine were tested in a small group of volunteers divided into two groups defined as “high-anxiety” and “low-anxiety” groups. The volunteers were females aged 18 to 22. Their level of anxiety was assessed by a manifest anxiety scale. Subjects received water, 50 mg of L-theanine or 200 mg of L-theanine solution once a week. Brain waves were measured 60 minutes after administration. The 200 mg dose (dissolved in 100 ml of water) resulted in significantly greater production of alpha waves than was observed in subjects receiving water. Greatest production was consistently seen about 40 minutes after L-theanine intake. The effect was dose-dependent. The researchers regarded the significantly increased production of alpha-brain wave activity as
an index of increased relaxation. More rigorous follow-up is needed.

A neuroprotective effect of L-theanine was observed in mice following middle cerebral artery occlusion. Size of cerebral infarct was reduced.

Recently, L-theanine was credited with enhancement of peripheral blood T cells, boosting immunologic memory. More research is indicated.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS
L-theanine is contraindicated in those who are hypersensitive to any component of an L-theanine-containing product.

PRECAUTIONS
Pregnant women and nursing mothers should avoid L-theanine supplements. Use of L-theanine supplements concomitantly with cancer chemotherapeutic agents must be done under medical supervision.

ADVERSE REACTIONS
There are no known adverse reactions.

INTERACTIONS

DRUGS
Doxorubicin and Idarubicin: L-theanine may enhance the antitumor effects of these drugs and may ameliorate some of their side effects.

DOSAGE AND ADMINISTRATION

L-theanine supplements have been available in Japan for some time for promotion of relaxation and modulation of mood. Doses used are between 50 and 200 mg, as necessary. L-theanine supplements are now available in the United States.

L-theanine is also available in some green tea preparations. The amino acid constitutes between 1% and 2% of the dry weight of green tea leaves. Two to three cups of green tea contain approximately 30-50 milligrams of the amino acid. Matcha, a variety of fine, powdered green tea used in the Japanese tea ceremony, has a higher amount of L-theanine when compared to other green tea varieties.

LITERATURE


L-Tryptophan

DESCRIPTION

L-tryptophan is one of the eight essential amino acids for humans (10 for children). It is the least abundant essential amino acid. An essential amino acid is an amino acid that the body cannot make, or if it can, it does not make it in sufficient amounts for all of its biological needs (for example, L-histidine and L-arginine for children). L-tryptophan is a protein amino acid, meaning that it is a building block of proteins. L-tryptophan also has other important functions. It is the precursor of the neurotransmitter serotonin, the pineal gland hormone melatonin (see Melatonin), the possible neuroprotectant kynurenic acid, vitamin B₃ (niacin or nicotinic acid and niacinamide or nicotinamide), and the coenzymes NADH (nicotinamide adenine dinucleotide) and NADPH (nicotinamide adenine dinucleotide phosphate).

A deficiency of niacin and/or L-tryptophan causes pellagra, which is characterized by the three Ds of dermatitis, diarrhea and dementia, and, if untreated for some time, a fourth D, death. Pellagra is a vitamin B₃ deficiency disease caused by dietary lack of niacin and protein, especially proteins containing the essential amino acid L-tryptophan. Because L-tryptophan can be converted into niacin, foods with L-tryptophan but without niacin, such as milk, prevent pellagra. However, if dietary L-tryptophan is diverted into the production of protein, niacin deficiency may still exist, leading to pellagra.

By the end of the 1980s, some millions of people, mainly women and mainly in the United States, were using supplemental L-tryptophan for a variety of reasons—premenstrual syndrome (PMS), sleep disorders, anxiety, depression, fibromyalgia, seasonal affective disorder (SAD) and chronic pain syndromes. Supplemental L-tryptophan was also used as an adjunct in the treatment of cocaine, amphetamine, alcohol and other drug abuse and for jet lag. In the context of the intensive care unit, some physicians used it as a sedative to help relax their intensive care unit patients with a substance that was less likely to suppress their respiration than a pharmaceutical sedative might. The physicians thought that this was particularly useful for those patients who had compromised respiration to begin with.

In fact, there were even some clinical studies that appeared to support some of the above uses of L-tryptophan.

In the fall of 1989, L-tryptophan supplementation was to see its darkest days. In October 1989, Dr. Philip Herzman and his colleagues in New Mexico met to compare notes on three female patients with unusual clinical presentations involving myalgia (muscle pain), weakness, oral ulcers, abdominal pain, skin rash and a striking increase in eosinophils (a subset of white blood cells) in their blood. These physicians recognized that all three patients developed these symptoms after using supplemental L-tryptophan, and they thought that the supplemental L-tryptophan might have caused the problem. They reported the illnesses and their suspected association of the illnesses to supplemental L-tryptophan to the New Mexico Health and Environment Department and the CDC (Centers for Disease Control and Prevention). The New Mexico Health and Environmental Department discovered several similar cases, almost all of which involved supplemental L-tryptophan. As awareness of the problem grew—the CDC notified all state health departments about a health problem possibly due to ingestion of supplemental L-tryptophan—a number of cases were reported from other states. In November 1989, the CDC proposed the name of eosinophilia-myalgia syndrome, or EMS, for the disease, since all the presumptive cases had both eosinophilia (elevation of eosinophils in their blood) and severe myalgia (muscle pain). Since trichinosis also causes eosinophilia and myalgia, the initial CDC surveillance definition of an EMS case required serological testing or a muscle biopsy to rule