



## L-Theanine

### Introduction

L-theanine ( $\gamma$ -glutamylethylamide) is a unique amino acid present almost exclusively in the tea plant (*Camellia sinensis*). It appears to only occur in three other species; one mushroom

species and two other species of the *Camellia* genus. Since tea is the second most consumed beverage in the world, a considerable amount of theanine is consumed daily throughout the world and is said to greatly contribute to the taste of green tea. Tea contains a number of constituents, including polyphenols, proteins, amino acids, organic acids, vitamins, minerals, and pigments. Theanine comprises 1-2 percent of the dry weight of tea leaves, makes up approximately 50 percent of the amino acids in tea, and is present as the free amino acid only – it does not occur in proteins. Theanine is synthesized in the root of the plant and concentrates in the leaves, where sunlight converts theanine to polyphenols. Because of this, some tea cultivators grow their plants out of direct sunlight to preserve the theanine content and thus the flavor.<sup>1</sup>

### Biochemistry and Pharmacokinetics

L-theanine was discovered as a constituent of green tea in 1949 by Sakato,<sup>2</sup> and in 1964 was approved as a food additive in Japan. It is a water-soluble compound and when ingested orally is absorbed in the small intestine. In rats, peak plasma concentration was found 30 minutes after oral dosing.<sup>3</sup> Theanine crosses the blood-brain barrier via the large neutral amino acid (leucine-preferring) transport system. Theanine, when reaching the brain, has been shown in rats to increase both serotonin and dopamine production.<sup>4</sup> Theanine is hydrolyzed in the kidney to glutamic acid and ethylamine by the enzyme glutaminase.<sup>3</sup>

### Mechanisms of Action

In the brain L-theanine increases dopamine and serotonin production,<sup>4</sup> although one study showed a decrease in serotonin in rats administered theanine.<sup>5</sup> Regardless of the mechanism, theanine increases alpha-brain wave activity, a sign of induced relaxation.<sup>6</sup>

L-theanine has been studied extensively for its effects on tumor cells and the sensitivity of those cells to chemotherapeutic agents. It appears theanine competitively inhibits glutamate transport into tumor cells, which causes decreased intracellular glutathione (GSH) levels. Theanine also inhibits the efflux of chemotherapeutic agents, such as doxorubicin, idarubicin, cisplatin, and irinotecan, causing them to accumulate in tumor cells. Theanine also protects normal cells from damage by these drugs via antioxidant activity, specifically by maintaining cellular GSH levels.<sup>7-10</sup>

The antioxidant activity of L-theanine has been studied in regard to its effect on the oxidation of LDL cholesterol. *In vitro* testing using malondialdehyde as a marker of lipid peroxidation demonstrated inhibition of LDL oxidation with theanine, although the effect was weaker than the potent antioxidant effect of green tea polyphenols.<sup>11</sup>

L-theanine may counteract the stimulatory effect of caffeine. In rats, theanine administered intravenously after caffeine dosing, and at approximately the same dose, blunted the stimulant effect of caffeine seen on electroencephalographic recordings. When given by itself in a smaller dose (20-40% of the original dose), theanine administration resulted in excitatory effects, suggesting a dual activity of theanine, depending on the dose.<sup>12</sup>

A dose-dependent hypotensive effect of theanine was seen *in vivo* in spontaneously hypertensive rats injected with L-theanine.<sup>13</sup> Glutamine (which is structurally similar to theanine) administration did not alter the blood pressure.<sup>14</sup>

## Clinical Indications

### Stress/Anxiety

Studies show L-theanine induces alpha-brain wave activity, which correlates with a perceived state of relaxation. A small Japanese study of university students showed oral L-theanine administration of 200 mg led to increased alpha-brain waves and a subjective sense of relaxation. Theanine administration caused a dose-dependent relaxed, yet alert, state of mind without sedation, beginning approximately 40 minutes after oral dosing.<sup>6</sup>

Green tea is often used as a relaxing beverage, although it can contain more caffeine than coffee. Theanine appears to counteract the stimulant effect of caffeine to some degree.<sup>12</sup>

### Hypertension

In studies of spontaneously hypertensive rats, L-theanine administration caused a significant reduction in blood pressure.<sup>15,16</sup> Whether humans will experience similar results has yet to be determined; however, theanine might find a place in antihypertensive treatment regimens.

### Cancer

Numerous *in vitro* and animal studies have investigated L-theanine's effect on cancer. Theanine decreased the size of ovarian tumors in M5076 ovarian sarcoma-bearing mice, when given in conjunction with chemotherapeutics, including doxorubicin, idarubicin, pirarubicin, cisplatin, and irinotecan.<sup>7-10,15</sup> L-theanine, given along with doxorubicin, reduced the size of ovarian tumors and decreased metastases to the liver as well.<sup>15</sup> In another study, theanine almost doubled the effect of doxorubicin in Erlich ascites carcinoma, while increasing the drug's concentration in tumor cells threefold.<sup>16</sup> It appears theanine exerts an additive effect along with chemotherapy by reducing transport of glutamic acid into the cell, decreasing GSH levels in the cell, and increasing the

concentration of the drug in tumor cells. Theanine also protects normal cells from damage by chemotherapeutic drugs.<sup>7-10</sup>

## Drug-Nutrient Interactions

L-theanine increases the activity of doxorubicin, idarubicin, pirarubicin, cisplatin, and irinotecan in tumor cells.<sup>7-10,15</sup>

## Side Effects and Toxicity

L-theanine is generally well tolerated, and has an LD<sub>50</sub> of greater than 5,000 mg/kg in rats. It is not mutagenic or carcinogenic in animals or bacteria.

## Dosage and Administration

For relaxation, 200 mg L-theanine can be taken 2-3 times daily. For cancer in conjunction with chemotherapy the dose is speculative, as no human studies have been performed. However, a dosage of 400-800 mg three times daily can be used safely.

## References

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