



NATURAL MEDICINE JOURNAL
RESEARCH GUIDE

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SUSTAMINE[®]
A DIPEPTIDE FOR INTESTINAL
AND IMMUNE HEALTH

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MORE THAN HALF of all Americans live with some form of a chronic condition, such as an autoimmune disease, diabetes, hypertension, obesity, or depression. An integrative approach to health aims not only to alleviate the outward symptoms of these illnesses but also to support the healthy structure and function of all the cells, tissues, and organs involved in the disease process.

Among the multitude of factors involved in the development and progression of chronic diseases is low-grade inflammation. Underlying inflammation are a myriad of physiologic changes, including alterations in the gut microbiome, intestinal barrier integrity, and immune function.

Because of the integral connections between gastrointestinal health, immune health, and chronic disease, strategies to supporting healthy digestive and immune function are at the heart of integrative medicine. Clinical approaches include lifestyle changes, therapeutic diets, and nutritional supplementation to synergistically support the health of the gastrointestinal and the immune systems.

Many supplements are available to support intestinal integrity and immune health, but one of the most fundamental and widely used is l-glutamine. This guide provides a refresher on the physiologic roles of l-glutamine and introduces an innovative ingredient that provides a highly absorbable and bioavailable source of l-glutamine—a dipeptide by the brand name of Sustamine®.

What is L-Glutamine?

L-glutamine is the most plentiful amino acid in the body, circulating in higher concentrations in the bloodstream than any other amino acid. Large amounts of l-glutamine are stored in skeletal muscle, with smaller amounts stored in the liver, brain, and stomach tissue.

L-glutamine is the primary source of metabolic fuel for enterocytes, lymphocytes, macrophages, and fibroblasts. It serves as a building block for protein synthesis and can be metabolized into glucose, nucleotides, or other amino acids. L-glutamine is one of three amino acids required for the production of the powerful cellular antioxidant glutathione.

L-glutamine is synthesized in the body, with skeletal muscle producing the greatest amount and the lungs producing the second largest amount. L-glutamine

Benefits of Sustamine®

- Made by fermentation (not synthetic)
- 100% pure powder (allergen-free)
- Vegetarian
- Non-GMO
- Stable at room temperature
- Soluble in cold water
- Transparent and tasteless when mixed with water
- Better absorbed than l-glutamine
- The only l-alanyl-l-glutamine with self-GRAS, Novel Food and TGA status
- Backed by human clinical research

synthesis is catalyzed by the enzyme glutamine synthetase and depends upon its precursor glutamate as well as ammonia, magnesium, and ATP.

Because of the significant body stores of l-glutamine and the ability for endogenous production, this amino acid was long thought to be nonessential in the diet. There are circumstances, however, when the body's demand for l-glutamine outpaces its supply.

L-glutamine is consumed by fibroblasts and other immune cells when there has been tissue injury. It is quickly depleted by traumatic injury, surgery, critical illness, or even exercise that is too strenuous.

Under these circumstances, the shunting of l-glutamine to tissue sites reduces its availability as a fuel for intestinal enterocytes. Increased intestinal permeability and compromised gut health are therefore common manifestations in patients who have recently experienced trauma, surgery, or critical illness.

The clinical advantages of l-glutamine stem from its fundamental role in cellular structure and function. Studies show that l-glutamine supplementation reduces infectious disease complications in critically ill patients, supports immune cell number and function, increases gut glutathione production, improves intestinal mucosal health, and improves intestinal barrier function.

Despite its many clinical applications and benefits, the stability, solubility, and absorption of l-glutamine are not ideal. The dipeptide l-alanyl-l-glutamine (Sustamine®) provides a supplemental source of l-glutamine that overcomes many key challenges.

What is Sustamine®?

Sustamine® is a dipeptide of two amino acids: l-alanine and l-glutamine. It is referred to in the literature as l-alanyl-l-glutamine, l-alanyl-glutamine, l-alanylglutamine, or alanyl-glutamine.

Sustamine® is produced by a unique fermentation process that creates a true dipeptide bond between the l-alanine and l-glutamine. It is a raw ingredient that is produced in Japan by Kyowa Hakko Bio Co., Ltd. Sustamine® is used by high-quality dietary supplement companies in formulations targeted to support hydration, exercise performance, intestinal health, and immune function.

Sustamine® is a source of supplemental l-glutamine that is stable when mixed with liquids or other nutrients, soluble in hot or cold water or drinks, transparent and tasteless when added to water, and highly absorbable and bioavailable.

Sustamine® Stability and Solubility

One of the challenges with free-form l-glutamine is its poor stability when mixed with liquids of various temperatures or pH. Internal studies conducted by the manufacturers of Sustamine® show that this dipeptide resists degradation and maintains its stability better than l-glutamine at room temperature over time. Internal studies also show that Sustamine® is stable in water up to 95° C. This means that you can be more confident that products containing

Sustamine® are delivering the amount of active ingredient listed on the label.

Another challenge with free-form l-glutamine is its poor solubility in liquids. Supplemental l-glutamine is often a powder to be mixed into water or another drink. L-glutamine can leave a gritty texture when mixed with cold water. Sustamine® manufacturer's internal data show that the dipeptide is soluble in cold liquids across a wide range of pH levels, making it easier to mix with liquids and more palatable to drink.

Intestinal Absorption of Sustamine®

Smaller than a complete protein, the Sustamine® dipeptide requires less energy for digestion and absorption than longer peptide chains. Interestingly, dipeptides are also absorbed more efficiently than single amino acids.

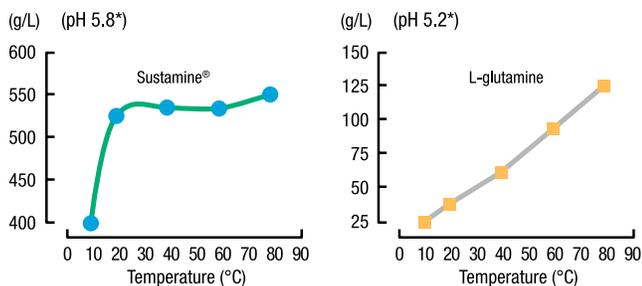
The reason that dipeptides absorb more efficiently than single amino acids is that both rely on transporter molecules to pass into intestinal cells. Single amino acids compete for transporters, whereas there is a specific dipeptide transporter for Sustamine®. That means that the Sustamine® dipeptide delivers two amino acids into systemic circulation for the same energy cost as one.

Human studies confirm that Sustamine® is more efficiently absorbed than l-glutamine alone. A 2012 study, published in *Nutrition Research*, compared the absorption of water (the control) to Sustamine® and an equivalent dose of l-glutamine. Compared with the single amino acid l-glutamine, Sustamine® increased

Sustamine® is soluble

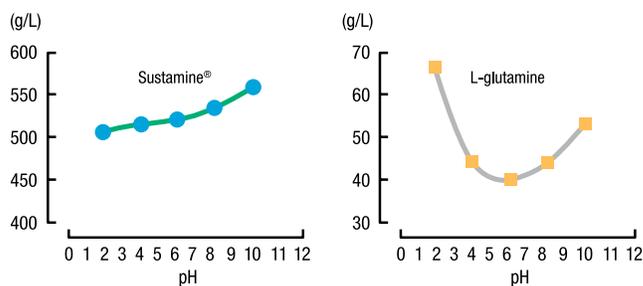
For patients who have a difficult time swallowing pills, Sustamine® offers the added benefit of dissolving completely in hot or cold liquids—so there is no gritty texture.

Temperature-dependent solubility



*pH when material is dissolved in water

pH-dependent solubility (20°C)



peak plasma l-glutamine levels more, maintained plasma levels longer, and achieved significantly higher mean area-under-the-curve plasma levels. Overall, Sustamine® was absorbed up to 224% better than l-glutamine alone.

Knowing that Sustamine® effectively transfers l-glutamine through the intestinal cells and into systemic circulation more effectively than l-glutamine alone might raise a logical question: how available is the l-glutamine in Sustamine® to the enterocytes of the small intestines?

While there are no direct studies to compare the oral availability to enterocytes of the l-glutamine in Sustamine® to the free-form of l-glutamine, plenty of studies confirm an equivalent or superior ability of Sustamine® to support intestinal mucosal and barrier function when delivered intravenously or in a formulation with total parenteral nutrition (TPN).

Enterocytes derive l-glutamine not only from the contents of the intestinal lumen but also from systemic circulation. Studies confirm that after Sustamine® is taken orally and absorbed, it readily dissociates into its free amino acids—l-glutamine and l-alanine. The free l-glutamine is then available for metabolic processes, including as an intestinal fuel.

Sustamine® and Gut Health

L-glutamine is the primary metabolic fuel for enterocytes, so these rapidly dividing cells of the small intestine utilize more l-glutamine than any other organ of the body. Within enterocytes, glutaminase

activity is high, and glutamine synthase activity is low, meaning that these cells must rely on a steady supply of l-glutamine. They absorb l-glutamine from two sources: the lumen of the gastrointestinal tract and the bloodstream.

L-glutamine is well known for its ability to support intestinal barrier function, but most clinicians don't realize that the research to support this comes mostly from studies of its use in TPN. Conventional TPN solutions do not contain l-glutamine and lead to adverse gastrointestinal effects, including gut mucosal atrophy, reduced immunoglobulin A (IgA) levels, and increased intestinal permeability.

Studies in animals and humans repeatedly show that adding supplemental l-glutamine to TPN mitigates many of TPN's adverse gastrointestinal effects. Because of its superior solubility and stability when compared with free-form l-glutamine, the Sustamine® dipeptide has been the l-glutamine source of choice for many of these studies.

Here we review the in vitro studies, animal studies, and human clinical trials related to the role of Sustamine® in supporting intestinal health.

In Vitro Studies

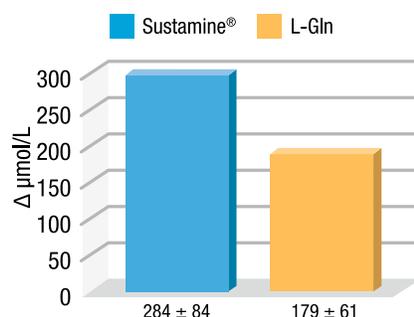
In vitro studies of l-alanyl-l-glutamine demonstrate that it is equally effective as l-glutamine to fuel enterocytes and support intestinal barrier function. A 2017 study, published in *Amino Acids*, found that the dipeptide had similar effects as free l-glutamine in porcine enterocytes

Dipeptide absorption research

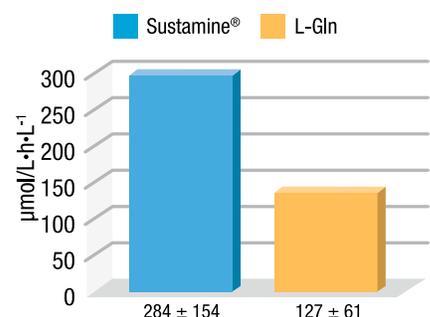
A crossover study utilizing a placebo control measured plasma L-glutamine concentrations. The study compared L-glutamine absorption levels between water (the control), Sustamine® and straight L-glutamine (L-Gln) and measured both mean peak increase and mean area under the curve (AUC) levels.

- Sustamine® showed statistically significant increases in L-glutamine peak plasma absorption levels
- Sustamine® maintained L-glutamine levels in the plasma longer (up to 4 hours) than L-Gln (up to 2 hours)
- Mean AUC measurements revealed statistically higher plasma L-glutamine levels for Sustamine® than L-Gln

L-glutamine peak plasma concentrations



L-glutamine AUC plasma concentrations



and could be substituted for l-glutamine as an energy source for intestinal cells.

Two studies published in 2013 (in *BioMedResearch International* and *The Journal of Infectious Diseases*) and an earlier study in 2006 assessed the effects of l-alanyl-l-glutamine and l-glutamine on intestinal epithelial cell lines exposed to *Clostridium difficile* toxin. Results of these studies were consistent, showing that both the dipeptide and the single amino acid reduced toxin-induced intestinal epithelial cell damage.

A 2019 study, published in the *Journal of Pediatric Gastroenterology and Nutrition*, investigated the effects of l-alanyl-l-glutamine intestinal cells exposed to pathogenic *Escherichia coli*. Results showed that l-alanyl-l-glutamine inhibited cell death, improved cell proliferation, and downregulated inflammatory pathways in infected cells.

Another 2019 study, published in *Biochemistry and Cell Biology*, evaluated the effects of l-alanyl-l-glutamine in bovine jejunum epithelial cells. Results showed that the dipeptide protected against intestinal inflammation when the cells were exposed to the bacterial lipopolysaccharide (LPS) endotoxin.

Animal Studies

Although the data from *in vitro* and animal studies don't always translate to clinical relevance in humans, these data do enlighten us about mechanisms of action and physiologic effects in living species. Studies of l-alanyl-l-glutamine have been conducted in several types of animals, including rats, hamsters, mice, and pigs.

Chemotherapy and TPN are both known to have adverse effects on the gastrointestinal tract. A 1996 study, published in *Nutrition*, showed that l-alanyl-l-glutamine maintained the intestinal mucosa and intestinal barrier function in rats receiving TPN and a chemotherapeutic agent. A 2008 study, published in *Cancer Chemotherapy and Pharmacology*, showed that l-alanyl-l-glutamine accelerated mucosal recovery, recovered mucosal glutathione stores, and reduced inflammatory parameters in hamsters with chemotherapy-induced oral mucositis.

L-alanyl-l-glutamine has been shown to reduce inflammatory markers and enhance mucosal recovery in a mouse model of colitis (published in 2013 in the *European Journal of Nutrition*). And a 2017 study, published in *Asian-Australas Journal of Animal Science*, found it to support intestinal barrier function and mucosal immunity in pigs.

L-glutamine is the primary metabolic fuel for enterocytes, so these rapidly dividing cells of the small intestine utilize more l-glutamine than any other organ of the body.

Human Studies

The effects of Sustamine® on gastrointestinal health have been evaluated in human clinical trials of patients with severe burns, HIV/AIDS, and gastrointestinal side effects of chemotherapy or radiation. In these clinical contexts, Sustamine® has been administered as part of enteral nutrition, as part of TPN, as a stand-alone intravenous (IV) therapy, and as an oral supplement.

A 2003 randomized controlled trial, published in the *Journal of Parenteral Enteral Nutrition*, evaluated supplementation with the dipeptide l-alanyl-l-glutamine in 40 people with severe burns. One group received standard enteral nutrition through tube-feeding, and the other group received the same nutrition enriched with l-alanyl-l-glutamine. One day after injury, all patients demonstrated evidence of increased intestinal permeability (increased lactulose/mannitol ratios). Within three days, the group receiving l-alanyl-l-glutamine demonstrated significantly less intestinal permeability and less endotoxemia than the control group. Also, the length of stay in the hospital was significantly shorter, and the cost of care was less, in those supplemented with l-alanyl-l-glutamine.

Two clinical trials have evaluated Sustamine® in patients with gastrointestinal side effects of chemotherapy or radiation. A 2009 randomized controlled trial, published in *Alimentary Pharmacology and Therapeutics*, evaluated the effects of IV l-alanyl-l-glutamine in 44 patients with gastric or colorectal cancer receiving chemotherapy. This study found that l-alanyl-l-glutamine (20 grams IV per day for 5 days) significantly reduced endotoxemia, nausea, vomiting, and diarrhea—suggesting that the dipeptide effectively protected against chemotherapy-induced intestinal permeability and gastrointestinal toxicity.

The clinical trial in patients with radiation-induced injury was a 2016 randomized controlled trial, published in *Nutrition in Clinical Practice*. The study

evaluated the effects of perioperative l-alanyl-l-glutamine-supplemented TPN in patients with intestinal obstruction induced by chronic radiation enteritis. Compared with the control, l-alanyl-l-glutamine-supplemented TPN significantly decreased intestinal permeability (based on lactulose/mannitol ratios) and boosted immune function.

Two clinical trials of oral Sustamine® supplementation have been conducted in patients with HIV/AIDS. Many patients with HIV/AIDS experience diarrhea and disruption of intestinal immunity and barrier function as a consequence of the disease pathology. A 2013 randomized, double-blind, placebo-controlled trial,

Sustamine® Supports Hydration, Metabolism, and Exercise Performance

Many of the benefits of Sustamine® stem from its ability to provide a more bioavailable source of l-glutamine, but the alanine portion of the dipeptide offers some advantages of its own. Alanine supports protein synthesis and is also involved in healthy glucose metabolism. The combination of l-alanine and l-glutamine as a dipeptide has been shown to enhance hydration and exercise performance.

Sustamine® supports hydration because of its interaction with ion transporters in the intestinal epithelia. Several human clinical trials of Sustamine® have found it to support hydration and exercise performance.

A 2010 study, published in the *Journal of the International Society of Sports Medicine*, reported that oral Sustamine® (0.05 g/kg and 0.20 g/kg) increased time to exhaustion in healthy men exposed to mild dehydration and endurance exercise.

Then a 2012 study, published in the *Journal of the International Society of Sports Medicine*, showed that rehydration with Sustamine® (1-2 grams in 500 mL of water) enhanced sports performance and visual reaction time better than rehydration with water alone in female basketball players.

Lastly, a 2016 study, published in the *European Journal of Sports Science*, reported that oral Sustamine® (600 mg or 2g) improved time to exhaustion in endurance athletes running at high-intensity on a treadmill for one hour.

published in *Arquivos de Gastroenterologia*, reported that ten days of oral l-alanyl-l-glutamine supplementation (24 grams per day) improved intestinal permeability and absorption, based on measurements of lactulose and mannitol excretion.

The other clinical trial in patients with HIV/AIDS was a 2004 randomized controlled trial, published in *Clinical Infectious Diseases*. Forty-one patients were divided into four groups for oral supplementation with glycine (control), l-glutamine (30 g/day), low-dose l-alanyl-l-glutamine (4 g/day), or high-dose l-alanyl-l-glutamine (44 g/day) for seven days. Results showed that l-glutamine and l-alanyl-l-glutamine supplementation both significantly improved diarrhea and absorption of antiretroviral drugs. Improvements in clinical and laboratory parameters were best in the high-dose l-alanyl-l-glutamine group and second best in the l-glutamine group.

Sustamine® and Immune Health

Gut health and immune health are intricately related. We have so far emphasized l-glutamine's role as a fuel for the enterocytes, but it also influences intestinal immunity. Just like enterocytes use l-glutamine as a fuel, lymphocytes, macrophages, and fibroblasts also utilize l-glutamine as a source of metabolic fuel and a source of nucleotides for rapid proliferation.

Immune cells cannot synthesize l-glutamine, so they rely on a steady supply from the bloodstream to respond to illness or injury. Animal studies have found that l-glutamine-supplemented TPN mitigates TPN's adverse effects on gut-associated lymphoid tissue (GALT). Here we review the human clinical trials related to Sustamine® and immune function.

Human Studies

Sustamine® has been evaluated for its effects on immune function in human clinical trials involving patients with multiple trauma, acute pancreatitis, and those undergoing surgery. In these contexts, it has been administrated as a supplement to TPN or as a stand-alone IV therapy.

A 1998 randomized controlled trial, published in the *Lancet*, compared l-alanyl-l-glutamine-supplemented TPN to standard TPN in 60 patients with multiple trauma and an expected survival of 48 hours. Compared with the control, patients receiving l-alanyl-l-glutamine supplementation experienced fewer cases of pneumonia, sepsis, and bacteremia, suggesting that the dipeptide supported immune function in critically ill patients.

Approved Structure-Function Claims for Sustamine®

- Sustamine® has superior absorption, stability, and solubility when compared with l-glutamine
- Sustamine® helps maintain glutamine balance during rigorous exercise
- Sustamine® may support exercise performance
- Sustamine® may support hydration
- Sustamine® helps to stimulate the immune system
- Sustamine® supports immune health
- Sustamine® supports the integrity of the gastrointestinal tract
- Sustamine® supports maintenance of healthy intestine function
- Sustamine® promotes the integrity and optimal function of the intestinal barrier

A 1998 randomized controlled trial, published in *Annals of Surgery*, evaluated the effects of l-alanyl-l-glutamine-supplemented TPN for five days in 28 patients undergoing elective abdominal surgery. Compared with patients receiving an isocaloric control, patients receiving the l-alanyl-l-glutamine supplementation showed improved nitrogen balance and improved lymphocyte recovery on day six. Also, the post-operative hospital stay was significantly shorter for the dipeptide group.

A 2008 study, published in *World Gastroenterology Journal*, evaluated the effects of IV l-alanyl-l-glutamine in 80 patients with acute pancreatitis. Patients received l-alanyl-l-glutamine dipeptide for ten days, beginning either on the day of admission or 5 days after hospital admission. Results showed that early administration of l-alanyl-l-glutamine reduced infection rates, complications, and mortality.

Finally, a 2011 study, published in *Acta Cirurgica Brasileira*, evaluated the effects of IV l-alanyl-l-glutamine given to children before surgery for cleft palate. Compared with the control group, children in the l-alanyl-l-glutamine group had significantly lower serum levels of C-reactive protein (CRP) during the post-operative period, suggesting attenuation of the inflammatory response to surgery.

Sustamine® in Clinical Practice

European organizations recommend the use of Sustamine® instead of l-glutamine for enteral and parenteral nutrition because of its superior solubility and stability. In the context of intestinal and immune health, most clinical trials of Sustamine® have administered the dipeptide in an IV solution. Some studies have administered it with enteral nutrition, and a select few have administered it as an oral supplement.

In everyday integrative health practice, the most convenient way to recommend Sustamine® is oral supplementation. Sustamine® is an ingredient that is combined with electrolytes in sports drinks or combined with herbs and vitamins in powders, capsules, tablets, drinks, and functional foods to support gastrointestinal and immune health.

The recommended oral intake of Sustamine® varies depending on the application. Clinical trials that show the dipeptide supports intestinal and immune health in patients with HIV/AIDS have administered daily amounts as high as 24-44 grams. Conversely, clinical trials in healthy athletes have used intakes as low as 600 mg to 2 grams. A consensus statement from a panel of experts in 2016 concluded that Sustamine® has self-GRAS status and can be safely added to functional foods in amounts that provide up to 6.9 grams of the dipeptide per day.

Most dietary supplements that contain Sustamine® deliver less than 5 grams of the dipeptide per serving. A person's metabolism, stress level, dietary habits, and health status determine their demand for l-glutamine, making it difficult to generalize an optimal daily amount. Further research is needed to determine what effects small daily intakes have on intestinal and immune health.

In sum, Sustamine® supports rehydration, exercise performance, intestinal mucosal integrity, intestinal barrier function, and immune health. Sustamine® is a reasonable consideration for any person experiencing physical or emotional trauma because of the increased demand for l-glutamine during catabolic stress. Sustamine® should be considered in any clinical situation where l-glutamine is indicated, as it is a highly stable, soluble, absorbable, and bioavailable source of this fundamental amino acid.

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