The Anti-infective and Anti-inflammatory Effects of Glutamine

Glutamine is the most abundant amino acid in the blood stream (30-35% of amino acid nitrogen in plasma) and fills a number of biochemical needs in the body. Glutamine is found most abundantly in high protein foods such as meat, fish, legumes, and dairy. Two particularly high vegetable sources are raw (uncooked) cabbage and beets. It is known that cooking can destroy glutamine, particularly in vegetables. Glutamine is a conditionally-essential amino acid, in that the human body can produce it endogenously. Deficiencies are prevalent, however, primarily as a result of cancer, burns, trauma, chronic protein catabolism and excessive exercise. While glutamine is largely formed and stored in skeletal muscle and in the lungs, it is the main metabolic fuel for enterocytes of the small intestine, lymphocytes, macrophages, and fibroblasts and plays a major role in the first line of immune defense in the intestine, as well as in the body as a whole.

Research suggests that glutamine is essential to the health and maintenance of the intestinal tract. In fact, the intestine, and particularly the small intestine, is the greatest user of glutamine in the body. The intestinal enterocytes absorb glutamine from the lumen of the gut and the bloodstream. The intestinal cell mitochondria then convert glutamine to glutamate, and then to alpha-ketoglutarate, which is used in the Krebs cycle for ATP production (Figure 1).

**Figure 1. Catabolism of L-glutamine**

Studies have shown that the level of stored glutamine drops significantly in humans following surgery, trauma, or burns, as well as during sepsis. Its deficiency has been implicated in immune dysfunction because it serves as a main precursor of nucleotide synthesis and also as an energy source for rapidly dividing cells, such as immune cells following an immune threat.

**Mechanisms of Action of Glutamine**

Lymphocytes use a large amount of glutamine, even in the resting state. However, they show no signs of glutamine synthetase activity in vitro, suggesting that lymphocytes are dependent upon pre-formed glutamine from other sources. Consequently, as lymphocytes are activated, their consumption of glutamine increases. Lymphocytes respond to glutamine by proliferating and producing more lymphocyte-derived cytokines. Glutamine is also required for the activation of T cells, possibly because it stimulates entry into the cell cycle and expression of the “late” activation markers, CD71 and CD45RO. It is also necessary for interleukin-2 production by splenic lymphocytes.

**Prevention of Microbial Translocation**

Glutamine’s positive effect on the GI tract appears to be due to its use as a food source by both intestinal immune cells (lymphocyte-rich Peyer’s patches) and mucosal cells. Intestinal epithelial cells contain very low levels of glutamine synthetase and hence are largely dependent on pre-formed glutamine from the diet or from endogenous synthesis. If glutamine is lacking in the diet, or if a person is being fed parenterally due to illness, intestinal cells will take glutamine from the bloodstream at the expense of muscle tissue, thus depleting the body’s stores. This depletion of glutamine from muscle is a major cause of cachexia observed in critically ill patients. When levels of glutamine drop, intestinal epithelial cells and lymphocytes begin to lose function, compromising the integrity of the epithelium and leaving the intestine vulnerable to microbial translocation (passage of bacteria or toxins into the bloodstream via the intestinal wall) and subsequent risk of sepsis. Microbial translocation is also suspected of being instrumental in chronic low-grade inflammatory states such as enteritis. Several factors can disrupt intestinal permeability leading to increased microbial translocation, including: Trauma, Infection, Starvation, and Chemotherapy.

Bacteria, fungi, and other toxins can translocate across the weakened mucosal barrier into the bloodstream, where they react with the reticuloendothelial system, stimulating production of cytokines via the hypothalamic-pituitary-adrenal axis. Cortisol is subsequently released from the adrenals, which increases glutaminase activity in intestinal enterocytes, thereby increasing breakdown of glutamine in the small intestine. This results in a progressive depletion of glutamine and glutathione which contains glutamine) from skeletal muscle, leading to oxidative muscle tissue damage.

Oral glutamine supplementation increases intestinal glutathione synthetase activity, improving the antioxidant capacity of the gut and increasing the mitogenic response to immune threats. Gut-associated lymphoid tissue (GALT)
requires glutamine for optimal function. GALT includes Peyer’s patches and lymphoid follicles scattered throughout the intestinal mucosa. It is in this tissue that B and T immune cells are primed against intestinal antigens, thus forming a “frontline” defense of memory cells that can be seeded to distant mucosal effector sites.

Maintenance of immune function and a healthy intestinal tract is vital following trauma or other problems that reduce glutamine. It is known that glutamine decreases the incidence of infection in trauma patients following surgery and reverses mucosal atrophy in animals being fed parenterally. Total parenteral nutrition (TPN) without supplemental glutamine leads to atrophy of small intestinal gut-associated lymphoid tissue (GALT), decreased levels of small intestinal IgA, and impairment of upper respiratory tract secretory IgA-mediated mucosal immunity. TPN with glutamine, however, attenuates these changes.

Physical Exertion and Immune Function

Heavy and prolonged physical exertion can put a major strain on the immune system and improper nutrition can compound this negative effect. Endurance athletes who overtrain tend to have higher rates of infectious diseases and allergies, particularly in the upper airways. In addition, lymph nodes may swell, and wound healing may be delayed. It has been reported that markers of immune function are suppressed in overtrained athletes compared with those training moderately. It is probable that chronic overexercising depletes glutamine from skeletal muscle so that the body is not able to recover before the next workout. Over time, this may reduce the amount of glutamine available to immune cells and fibroblasts, weakening the immune system. Interestingly, when a diet containing glutamine alone was compared with a diet containing a mixture of glutamine, arginine, glycine, and omega-3 fatty acids, glutamine was as effective as the mixture in increasing B and T cell numbers in Peyer’s patches and spleen, and in increasing intestinal IgA content.

Mechanisms of Action of Cabbage: A Glutamine-Rich Food with Known Immunoprotective Properties

In addition to the obvious connection between the benefits of cabbage in improving immune function and its rich glutamine content, there are other factors within this whole food that contribute to its inherent immunoprotective properties. Cabbage stimulates the production of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), important players in antitumor, antiviral, immunoregulatory, and inflammatory responses. Further, cabbage contains glucosinolates and their breakdown products that show clear benefits in optimizing immune function by altering the induction of glutathione S-transferase (GST), NADPH, and quinone oxidoreductase (NQO). The GST family of detoxification enzymes are responsible for conjugating electrophilic compounds with glutathione, creating a more water-soluble, and usually non-cytotoxic compound to be excreted. The flavoprotein NQO functions as a catalyst for the reduction of a wide range of quinones, quinone imines, and azo dyes via a two-electron transfer. Researchers speculate that the protective action of NQO is a result of its successful competition with single-electron reduction reactions and the inhibition of oxidative metabolic intermediates. This augmentation in free radical production reduces the total burden placed on the immune system.

Known Medicinal Constituents in Cabbage

- 4-Me-glucobrassicin
- 4-OH-glucobrassicin
- Dithiolthiones
- Flavonoids
- Glucoiberin
- Gluconapin
- Gluconolactone
- Indole-3-carbinol
- Oxazolidinethione
- Progoitrin
- Sinigrin
- Thiocyanates
- Glutaminase

Indications for Use of Glutamine & Glutamine-Rich Foods

- Bone marrow transplantation
- Compromised immune function
- Critical illness
- Gastric hyperacidity
- Gastritis
- High amounts of athletic training, as for the Olympics
- High stress
- Intestinal ulcer
- Parenteral feeding
- Post-surgery
- Trauma

Research

In the laboratory

The mechanism by which glutamine modulates immune function in the gut has been explored in infant rats and in cultures of human intestinal epithelial cells (enterocytes). In infant rats dietary glutamine was both directly related to body growth and intestinal villus height, and inversely related to the lipopolysaccharide (LPS) induced inflammatory response. The mediator CINC (intestinal cytokine-induced neutrophil chemoattractant) was significantly decreased, and MPO (a marker of tissue injury) and TNF-α were markedly decreased in proportion to dietary content of glutamine. These effects were stronger in the intestine than in the plasma.

Caco-2 cells, incubated with various concentrations of glutamine and stimulated with LPS, which induces production of interleukin-8 (IL-8). IL-8 production was inversely related to glutamine concentration, a doubling of glutamine decreasing IL-8 production by a factor of 3.5. Among 54 inflammation-related transcription factors, STAT-4 was the only one identified as mediating this result. Further exploration of this mechanism showed that glutamine activated the inhibitor of the xB (IxBv) nuclear factor-xB signaling pathway. These researchers also noted a reduced capacity of immature enterocytes to respond to glutamine deprivation with increased synthesis of IxBv. These findings suggest that glutamine might provide a check on destructive chronic inflammatory conditions such as enteritis and that infants might be provided with an enhanced acute immune response in spite of glutamine deprivation while their immune systems are developing.

Cabbage and immune function in animals

Komatsu et al. administered cabbage juice to normal and hepatome-bearing rats. In this study, cabbage juice stimulated tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in the normal rats but failed to do so in the hepatome-bearing rats, whose levels of these enzymes were already elevated. The cabbage demonstrated immune stimulatory properties which the authors speculated were due to some “unknown” effective component that can be absorbed from the GI tract to stimulate production of TNF-α and IL-1. This component may be glutamine, although other functional constituents within cabbage cannot be ruled out. TNF-α and IL-1 are the primary cytokines produced by activated macrophages. Additionally TNF-α plays an important role in antitumor, antiviral, immunoregulatory, and inflammatory responses.
Glutamine

The first step in the production of TNF-α is the cytokine or biological response modifier pretreatment referred to as priming. For the priming step, normal and tumor-bearing rats were fed either juice or distilled water (control). Peritoneal macrophages were harvested four hours after ingestion of juice. The second step, triggering, involves a lipopolysaccharide treatment. In this step, cabbage was homogenized in an equal weight of distilled water and centrifuged to obtain juice (liquid fraction). Cells were then processed, cultured, and treated with a lipopolysaccharide. In normal rats, the production of TNF-α and IL-1 in response to the lipopolysaccharide was significantly enhanced by cabbage juice. TNF-α production was 380% greater in the juice-fed rats than in the control group. The differences did not reach significance in tumor-bearing rats, most likely because they were already producing high levels due to the implanted tumorous cells. Some studies suggest that TNF-α has a significant impact on intestinal function and integrity which ties closely to immune function. It is interesting to note here that glutamine is the primary respiratory fuel for both enterocytes and lymphocytes.

Glutamine and immune function in animals

In mice, a glutamine-enriched diet enhanced the ability of T-lymphocytes to respond to mitogenic stimulation. Mice were fed either a control diet (19.6 g glutamine/kg), a glutamine-enriched diet (54.8 g glutamine/kg), or an alanine/glycine-enriched diet (13.3 g glutamine/kg). The proportion of CD4+ and CD8+ cells was significantly greater in the spleens of mice fed the glutamine-enriched diet than in those of mice fed the control or alanine/glycine-enriched diets. As shown in Table 1, when spleen lymphocytes in the mice were mitogenically stimulated with concanavalin A, the mice fed the glutamine-enriched diet had:

- The greatest T-lymphocyte activity
- Increased thymidine incorporation
- Greater expression of the interleukin-2 α-subunit
- Increased interleukin-2 production

In addition, concanavalin A significantly increased the proportion of spleen lymphocytes expressing CD25 in all diet groups, but the increase was greatest in the mice fed the glutamine-enriched diet.

### Table 1. Concanavalin A-stimulated thymidine incorporation, CD25 expression, and cytokine production by spleen lymphocytes from mice fed control, glutamine-enriched, or alanine/glycine-enriched diets for 2 weeks.56

<table>
<thead>
<tr>
<th>Concanavalin A</th>
<th>Control</th>
<th>Glutamine</th>
<th>Alanine/Glycine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymidine Incorporation (μg/well)</td>
<td>1.6±0.44</td>
<td>2.7±0.86</td>
<td>1.7±0.42</td>
<td>NS</td>
</tr>
<tr>
<td>Stimulation index</td>
<td>9.7±4.19</td>
<td>56.1±17.9</td>
<td>6.8±3.13</td>
<td>NS</td>
</tr>
<tr>
<td>CD25 (%)</td>
<td>7.9±6.7</td>
<td>9.4±0.3</td>
<td>7.5±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>CD4+CD25 (%)</td>
<td>31.7±5.4</td>
<td>61.7±3.9</td>
<td>30.5±4.9</td>
<td>0.02</td>
</tr>
<tr>
<td>CD8+CD25 (%)</td>
<td>4.9±4.4</td>
<td>6.3±0.5</td>
<td>4.9±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>CD8+CD4+CD25 (%)</td>
<td>18.0±0.9</td>
<td>65.9±2.1</td>
<td>19.9±2.2</td>
<td>0.018</td>
</tr>
<tr>
<td>Interleukin-2 (μg/L)</td>
<td>2.3±0.5</td>
<td>2.5±0.8</td>
<td>3.4±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Interleukin-4 (μg/L)</td>
<td>3.1±1.4</td>
<td>1.6±1.8</td>
<td>2.9±1.3</td>
<td>0.028</td>
</tr>
</tbody>
</table>

The observed increase in production of interleukin-2 and interferon-γ with increasing availability of glutamine strongly suggests an enhanced ability of the host to combat a variety of infections and possibly even the growth of tumors. The results of this study are supported by similar research in piglets fed glutamine after being subjected to E. coli infection. Dietary glutamine probably exerts most of its effect on lymphocyte function at the level of the gut-associated immune system since plasma glutamine concentration was not shown to be significantly different in mice fed the control vs. those fed the glutamine-enriched diet. Conversely, a homoeostatic mechanism in mice may keep plasma levels of glutamine constant at the expense of other tissues, such as muscle.

Female mice fed a glutamine-rich diet showed an increase in the total number of T and B lymphocytes in intestinal Peyer's patches, as well as increases in CD4+ and CD8+ lymphocyte subpopulations. The reduction in T and B cells caused by injection of lipopolysaccharide (endotoxemia) was significantly inhibited by glutamine (Figure 2). In addition, endotoxemia caused a 42% decrease in glutathione in control mice but not in glutamine-treated mice.

It appears that glutamine may prevent lipopolysaccharide-stimulated lymphocyte atrophy in Peyer's patches in part by increasing the glutathione content of the patches (Figure 3). This was supported by injecting mice with buthionine sulfoximine, a specific inhibitor of glutathione synthesis, which also decreased B and T cell numbers. The results of this study suggest that oral glutamine may be suitable for improving intestinal immunity in immunocompromised patients.

**Figure 2. Effect of glutamine on total number of T and B cells of Peyer's patches in healthy (control, glutamine [GLN]; n=8) or endotoxemic mice (control+lipopolysaccharide [LPS], GLN+LPS; n=5). Data are expressed as mean +/- SD. * P < .05 vs. control group. ** P < .01 vs. control group.**
GSH in PP

Perhaps the strongest evidence from animal studies for the role of glutamine in immune function is a study by DeWitt et al.44 These researchers immunized mice against pneumonia bacterial polysaccharide-containing liposomes and then fed the animals enterally or parenterally for five days, supplementing one parenterally-fed group with 2% glutamine. A negative control group was not immunized. The mice were then injected with a LD90 dose of Pseudomonas pneumonia bacterium (the amount known to kill 90% of non-immunized normal mice). While immunization reduced mortality in all groups, survival was significantly lower in mice fed parenterally without glutamine supplementation. Parenteral glutamine, however, preserved the immunization effectiveness seen in enterally fed and immunized animals, suggesting that depressed immunity due to parenteral feeding is a result of glutamine depletion (Figure 4).

**Glutamine and immune function in humans**

Infection is a major concern in seriously injured patients, and it is most likely related to decreased immune function in these patients combined with translocation of gram-negative bacteria from the gut.45,46 Glutamine deficiency is suspected in both of these processes because it is the preferred respiratory fuel for both lymphocytes and enterocytes.

Houdijk et al.47 examined the effect of glutamine fed enterally to trauma patients for five or more days following their injuries. Twenty-nine out of 60 patients received glutamine supplementation while the rest received a balanced, isonitrogenous, isocaloric enteral feeding regimem. Dramatically, the patients receiving glutamine had a much lower incidence of pneumonia, bacteraemia, and sepsis compared to the control group (Table 2). Because the majority of bacteraemia and sepsis cases involved gram-negative bacteria, the researchers believed glutamine was functioning by preventing bacterial translocation in the gut.

Low plasma and tissue levels of glutamine in critically ill patients suggests a demand for the amino acid that is not met by the body's available supply. Glutamine deficiency may compromise recovery in such patients, resulting in prolonged illness and an increase in mortality. In a block-randomized, double-blind treatment study,48 the role of glutamine on recovery and survival in 84 critically ill patients being fed parenterally was tested. Those patients supplemented with glutamine had better survival rates at 6 months, and greater rates of recovery.
Glutamine

as indicated by a 50% reduction in ICU and hospital costs per survivor.  

Following allogeneic bone marrow transplantation, glutamine-supplemented parenteral nutrition significantly improved nitrogen retention and decreased the incidence of clinical infection and microbial colonization in patients vs. parenteral nutrition without glutamine supplementation in a double-blind, randomized, controlled clinical trial. Only three of 24 (12.5%) experimental patients developed clinical infection compared with nine of 21 (43%) in the control group \( p=0.002 \). Additionally, the hospital stay of experimental patients was significantly shorter than that of the controls \( 29\pm1 \text{ day vs. } 36\pm2; p=0.017 \). The two groups had no differences in incidence of fever, antibiotic requirements, or time to neutrophil engraftment.

There is a cause and effect question between glutamine depletion and inflammation in reference to gut permeability and villus morphology. Is it inflammation or depletion that causes increased permeability, and which is responsible for villus atrophy? A human study of 26 patients requiring pre-operative TPN sought to resolve this question. Inflammatory markers, nutritional status, glutamine concentrations in plasma and gut mucosa, gut permeability, and mucosal morphology were assessed. The results demonstrated that inflammation was solely associated with glutamine depletion and increased intestinal permeability, while nutritional depletion alone was correlated with villus height.

Enteral infant formulas

Enteral infant formulas are usually very low in glutamine, although the amino acid is considered to be "conditionally essential" in premature, low birth weight babies (in whom body stores of glutamine are low and vulnerability to infection is high). Neu et al. examined glutamine supplementation in 68 very low birth weight neonates randomly assigned to receive either glutamine-supplemented premature formula or standard premature formula between days 3 and 30 post partum. Hospital-acquired sepsis was 30% in the control group and only 11% in the supplemental group \( p=0.048 \). The estimated odds of developing sepsis were 3.8 times higher for infants in the control group. Enteral feedings were better tolerated by the infants when receiving glutamine-supplemented formula. This research indicates that the addition of glutamine or high-glutamine whole food sources to infant formula is highly beneficial.

Bacterial infection in burn victims

Saito et al. revealed that supplemental glutamine augments the bacterial killing function of neutrophils in post-operative patients. In the presence of glutamine, neutrophils show increased phagocytosis and dose-dependent increases in the production of reactive oxygen intermediates. Glutamine has been shown to enhance the bactericidal function of neutrophils to Staphylococcus aureus infection in burn patients. Burn patients are particularly vulnerable to bacterial infection, and neutrophils isolated from them have impaired bactericidal activity. Neutrophils were isolated from 12 burn patients at several times post-burn and analyzed in vitro for their ability to kill S. aureus in the presence or absence of glutamine. Bacterial killing, as determined by surviving bacteria, reached normal or above normal levels for neutrophils treated with glutamine compared...
with neutrophils from normal patients. Glutamine had no effect on bacterial growth in the absence of neutrophils.

In patients with advanced esophageal cancer undergoing radiochemotherapy, glutamine supplementation prevented a reduction in the lymphocyte count and lymphocyte blast formation. Gut permeability was also improved in glutamine-supplemented patients, as indicated by decreased urinary excretion of orally-administered phenolsulfonphthalein (phenol red).

**Rationale for Administering Glutamine within a Whole Food Matrix for Optimal Immune Function**

Given the complexity and overlapping functions of the many arms of the immune system, it is unlikely that a single nutrient or mechanism of action of a functional compound is totally responsible for the impact that a food such as cabbage has on optimizing the immune response. As such, it is important to understand and emphasize the known facts about the actions of a single component in cabbage, such as glutamine, to attempt to connect the effects of other known compounds (such as glycosylated flavonoids and glucosinolate products) that affect immune function via an entirely different mechanism of action.

It appears that administering a vegetable that contains glutamine, in addition to other known tertiary compounds that serve to optimize immune function, would likely offer a greater effect than the sum of the individual components found within the food.25

**Overview**

These clinical results, coupled with the results of earlier trials, strongly suggest that Glutamine-rich foods, and particularly cabbage:

- Support immune function, especially in trauma and critically ill patients, and in high-training athletes76-79
- Inhibit oxygen free radical formation that causes inhibition of neutrophil bactericidal activity; reduce proliferation of T and B lymphocytes; and inhibit natural killer cell cytotoxic activity80-83
- Protect and improve the function of the gastrointestinal tract84-85
- Help prevent clinical infection related to bacterial translocation across the gut wall86-87
- Improve healing of the small intestinal mucosa after chemotherapy85
- Protect lymphocytes and attenuate gut permeability during radiochemotherapy86

**Contraindications:** None known

**Side Effects:** None known

**Possible Interactions with Drugs:** Cabbage may compromise the effectiveness of warfarin due to its high vitamin K content. Cabbage may also induce the hepatic metabolism of certain medications including warfarin, phenacetin, oxazepam, antipyrine, 7-ethoxycoumarin, hexobarbital, and acetaminophen 90

**Possible Interactions with Herbs and other Dietary Supplements:** None known

**Possible Interactions with Disease States:** Consumption of cabbage may worsen goiters and hypothyroidism.

**Recommended Mode of Administration:**

- Eat a diet high in glutamine-rich foods (raw cabbage, beets, meats, fish, legumes, and dairy) in patients with cancer, gastrointestinal dysfunction and/or compromised immune function.
- If necessary, add supplemental glutamine, 1.5-6 grams daily, divided into several doses) with glutamine-rich foods.

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**References**

Glutamine
