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REVIEW ARTICLE

The Vital Role of Glutamine in Monogastric Animals: More Than a Non-Essential Amino Acid

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ABSTRACT

Glutamine is a conditionally essential amino acid with fundamental roles in animal physiology. It acts as a primary energy source for rapidly dividing cells, including those in the gut and immune system. Beyond energy production, it is a crucial building block for proteins, nucleotides for DNA/RNA synthesis, and the potent antioxidant glutathione. During metabolic stress such as illness, trauma, or intense exercise, the body's demand for glutamine can exceed its production capacity, making dietary supplementation necessary. However, the free form of glutamine is highly unstable in solution, which limits its practical use. To address this, stable synthetic dipeptides like alanyl-glutamine have been developed to enhance glutamine's delivery, stability, and bioavailability. This review comprehensively examines the critical functions of glutamine, its distribution across different tissues, and the key challenges in its supplementation. A deeper understanding of glutamine metabolism aids in developing effective nutritional strategies to optimize its utilization, thereby supporting animal health, performance, and recovery.

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INTRODUCTION

Glutamine (Glu) is unequivocally an essential amino acid and acts as a vital fuel source for a wide range of cells, particularly epithelium and immune cells (Zhang *et al*., 2008). Undeniably, it plays vital physiological roles in a wide range of metabolic processes. It acts as an intermediator in energy metabolism and serves as a fundamental component for synthesizing peptides, non-peptides, nucleotides, glutathione, and neurotransmitters (Albrecht *et al*., 2010). In animal body, Glutamine is most enrich free amino acid, with 5-carbon amino acid and two amino groups (Fürst, 1983). Glutamine constitutes over 50% of skeletal muscle in free amino acid pool (Bergström *et al*., 1974) 25% of plasma free AA (Ahlman *et al*., 1994), and surpasses all other amino acids by a concentration of 10 times greater in the cerebrospinal fluid (Chaudhry *et al*., 2002). The primary metabolic function of Glu metabolism was firstly recognized by Sir Hans Krebs in 1935 due to its cohesion between tissues and across species, indicating its significance in cellular functions (Brosnan, 2001). While, in 1990 by Lacy and Wilmore it was proposed as conditionally essential AA (Lacey and Wilmore, 1990). The re-categorization of Glu was prompted by the observation of decreased plasma levels during catabolic stress. This suggests that glutamine production may not meet the requirement of body, necessitating the provision of an external supply (Coster *et al*., 2004). Unfortunately, Glu is well-known unstable when in solution, leading to the formation of toxic byproducts upon decomposition. As a result, solutions of nutrients that contain glutamine tend to have comparatively a short half-life. This has prompted the development and commercialization of more stable dipeptides that incorporate glutamine, providing a solution to the instability issue (Zhang *et al*., 2008). In the bodies of healthy individuals weighing approximately 70 kilograms, there is an estimated 70 to 80 grams of glutamine dispersed throughout various tissues and organs of its body (Newsholme *et al*., 2003). Through isotopic and pharmacokinetic methods, researchers have estimated that the human body's natural production of glutamine ranges from 40 to 80 grams per day (Wernerman, 2008). Glutamine concentration in plasma, derived from blood samples collected after a 12-hour fasting period, typically ranges from around 500 to 800 µM/L. This level accounts approximately 20% of the whole free amino acid pool, present in blood (Roth, 2008). In tissues such as liver and skeletal muscles, the glutamine content is notably elevated compared to plasma, approximately 40 to 60% of the overall amino acid pool (Cruzat and Newsholme, 2017). In

both, tissues and plasma, the glutamine content is remarkably increased as ranging from 10 to 100 times greater than any other AA (Labow *et al*., 2001).

Functions of glutamine: Glutamine shows a determined function in the body's energy metabolism pathways. It's not only a subunit of various essential molecules such as glutathione, neurotransmitters, and nucleotide bases but also shows a productive role in the body's acid-base balance maintenance and detoxifying ammonia. In the field of clinical practice, there is an increasing acknowledgement of the potential impact of providing glutamine-supplemented nutritional support on modulating the body's response to critical illness (Coster *et al*., 2004). Glutamine (Glu), a non-essential amino acid, plays various significant roles in the body. It has been recognized as an energy source for enterocytes and immune cells and is involved in the synthesis of important molecules such as purines and pyrimidines. Additionally, glutamine modulates protein turnover and contributes to processes like gluconeogenesis, acid-base balance, and redox homeostasis. Overall, it serves as an essential precursor for various biologically vital molecules, making it indispensable for human health (Souba, 1993).

Because of carbon skeleton and two active groups, glutamine acts as a critical nitrogen and carbon source, contributing to the swift turnover of the plasma Glu pool in the body (Cheng *et al*., 2012). In a number of studies using glutamine tracers in the human body, it has been demonstrated that as much as 30% glutamine pool is utilized for macromolecules synthesis (Biolo *et al*., 2005). The metabolic pathways of glutamine metabolism in humans have been extensively examined. As a result, glutamine was recorded as the most abundant and versatile amino acid in humans, is essentially involved in intermediate metabolism. It facilitates nitrogen exchange between organs via ammonia (NH_3) transport among tissues, contributes to pH regulation and acts as a precursor of diverse metabolites (Cruzat *et al*., 2018). Almost in every cell, Glu serves as a raw material for nucleotides production such as purines, pyrimidines, and amino sugars, as well as for producing nicotinamide adenine dinucleotide phosphate (NADPH), antioxidants, and various other essential components required for protecting the structural and functional integrity of cell membrane (Curi *et al*., 2016). During some conditions such as sepsis, recovery from blisters or operation, malnutrition, and heavy physical exercises, immune cells such as lymphocytes, neutrophils, and macrophages exhibit a pronounced utilization of glutamine, which exceeds their consumption of glucose (Cruzat *et al*., 2014, Newsholme *et al*., 2003). Glutamine participates in a wide range of physiological functions (Fig. 1). Its roles extend from energy provision to critical functions in intestinal health maintenance, modulating the immune system, and providing antioxidant protection, which collectively are vital for overall animal health (Murakami *et al*., 2007). It was stated that Glu significantly affects the development of the intestine. In broilers, the gastrointestinal tract experiences its most rapid growth during first week of their life (Zavarize *et al*., 2011). Furthermore, research has indicated that adding L-Glu to the diet of turkey poults can results in an increased height of the intestinal villi. This is thought to occur through the stimulation of gut cell growth, which plays a significant role in protecting gut integrity, intestinal barrier function, and facilitating the regeneration of gut mucosa. These mechanisms are particularly significant in the prevention of bacterial infections (Sakamoto *et al*., 2011). Glutamine has the potential to act as a signaling molecule or regulator, which may results in increased proteins synthesis and decreased the breakdown of proteins in the skeletal muscle of young broilers (Haussinger *et al*., 1994).

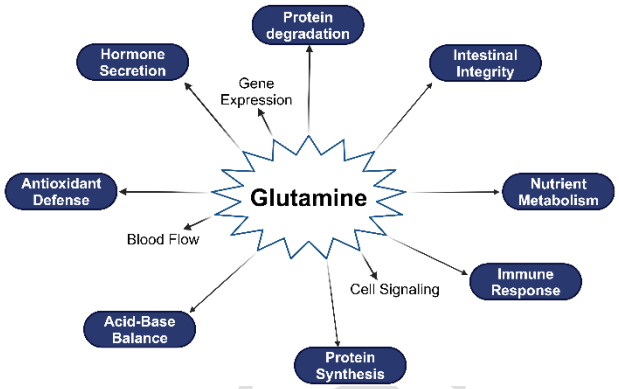

Fig. 1: Glutamine's function in animal body.

This schematic illustrates the central importance of glutamine, which acts as a critical substrate or signaling molecule in a diverse array of biological mechanisms. Key functions including protein synthesis, intestinal integrity, immune response, antioxidant defense and nutrient metabolism, among others, underscoring its systemic significance.

Metabolism of glutamine: Glutamine is an important L-α-amino acid with a relatively small molecular weight of 146.15 kDa. Its composition is primarily made up of carbon (41.09%), hydrogen (6.90%), oxygen (32.84%), and nitrogen (19.17%). It contains five carbon atoms and plays essential roles in various biological processes. Based on its physiological pH, Glutamine also known as glutamate, is considered a neutral amino acid. Interestingly, despite being classified as a non-essential amino acid from a nutritional perspective, it is still classified as neutral Glutamine possess two distinct amino groups, named as an α-amino group and the easily-hydrolysable side-chain amide group. These characteristics are pivotal in facilitating glutamine's role as a transporter of nitrogen and a carrier of NH_3. Glutamine, an essential proteinogenic amino acid, is actively aid in synthesis of proteins within the body. It makes up approximately 5 to 6% of the total bound amino acids present (Roth, 2008, Labow *et al*., 2001). In the process of glutamine metabolism, several enzymes play fundamental roles. The intracellular enzymes glutamine synthetase (GS, EC 6.3.1.2) and phosphate-dependent glutaminase (GLS, EC 3.5.1.2) are of particular importance. Glutaminase aids in catalyzing the reactions that create glutamine from an ammonium ion (NH^{4+}) and glutamate via ATP consumption. In addition, GLS facilitates glutamine hydrolyzation, converting it into glutamate and ammonium ions once again (Tan *et al*., 2017). Regarding the intracellular location, it is notable that GS (glutamine synthetase) is primarily present in the cytosol, while the active form of GLS is primarily localized

within the mitochondria. This distribution aligns with the specific functions of these enzymes within the cell. The GS plays a vital role in producing glutamine, which is used as a unit for cytoplasmic proteins and nucleotides, essential for a number of cellular functions. Meanwhile, glutaminase (GLS) facilitates the glutamine to glutamate conversion, a pivotal step that allows glutamate to enter the tricarboxylic acid cycle (TCA) at 2-oxoglutarate, providing the cell with both an energy source and key metabolic intermediates. This interplay between GS and GLS highlights their significance in regulating cellular metabolism and protein synthesis as shown in Fig. 2 (Curi *et al*., 2016). Glutamate itself is produced from 2-oxoglutarate NH_4 either through the enzymatic action of glutamate dehydrogenase, or via the breakdown of other amino acids, such as branched-chain amino acids (BCAAs), with a particular emphasis on leucine (Tan *et al*., 2017, Holeček, 2018). A number of researches on rats have revealed that Branched-Chain Amino Acids (BCAAs), particularly leucine, undergo transamination with α-ketoglutarate to produce glutamate as the primary metabolite. Subsequently, this glutamate combines with free NH_3 and, through the action of the enzyme GS, forms glutamine (Cruzat *et al*., 2014).

The glutamine concentration in tissues and blood are influenced by the activities of GS or GLS. In catabolic conditions such as cancer, sepsis, infections, surgeries, traumas, and intense or prolonged physical exercise, the body's endogenous synthesis of glutamine is insufficient to meet its demands (Leite *et al*., 2016). In certain deficient conditions, glutamine can play the role of a conditionally essential amino acid. It does this by increasing the GLS expression while inhibiting GS action (Labow *et al*., 2001). It is essential to highlight that despite the reduction in plasma glutamine concentration from the typical range of 500–800 µmol/L to 300–400 µmol/L, the effect on cells that depend on this amino acid, is relatively minimal in terms of their proliferation and function (Cruzat *et al*., 2018). While, high levels of tissue catabolism result in a decrease in glutamine levels in human tissues, particularly in muscles and liver tissues. This reduction in glutamine concentration has a widespread impact on the body, as glutamine act significantly in providing nitrogen atoms for the purines synthesis, pyrimidines, and amino sugars (Curi *et al*., 2016). The continuously higher glutamine degradation in these tissues can widely affect various metabolic reactions and mechanisms that rely on glutamine accessibility, ultimately leading to a state of immunosuppression. In recent studies, it has been found that bacterial infections, specifically *Escherichia coli*, have the capability to modify their metabolic pathway in order to utilize glutamine as a mechanism to mitigate the effects of acid stress and copper toxicity (Djoko *et al*., 2017, Wernerman, 2014). The bacterial pathogens have the ability to adapt and survive by modifying fundamental metabolic pathways crucial for combatting host-imposed antibacterial approaches.

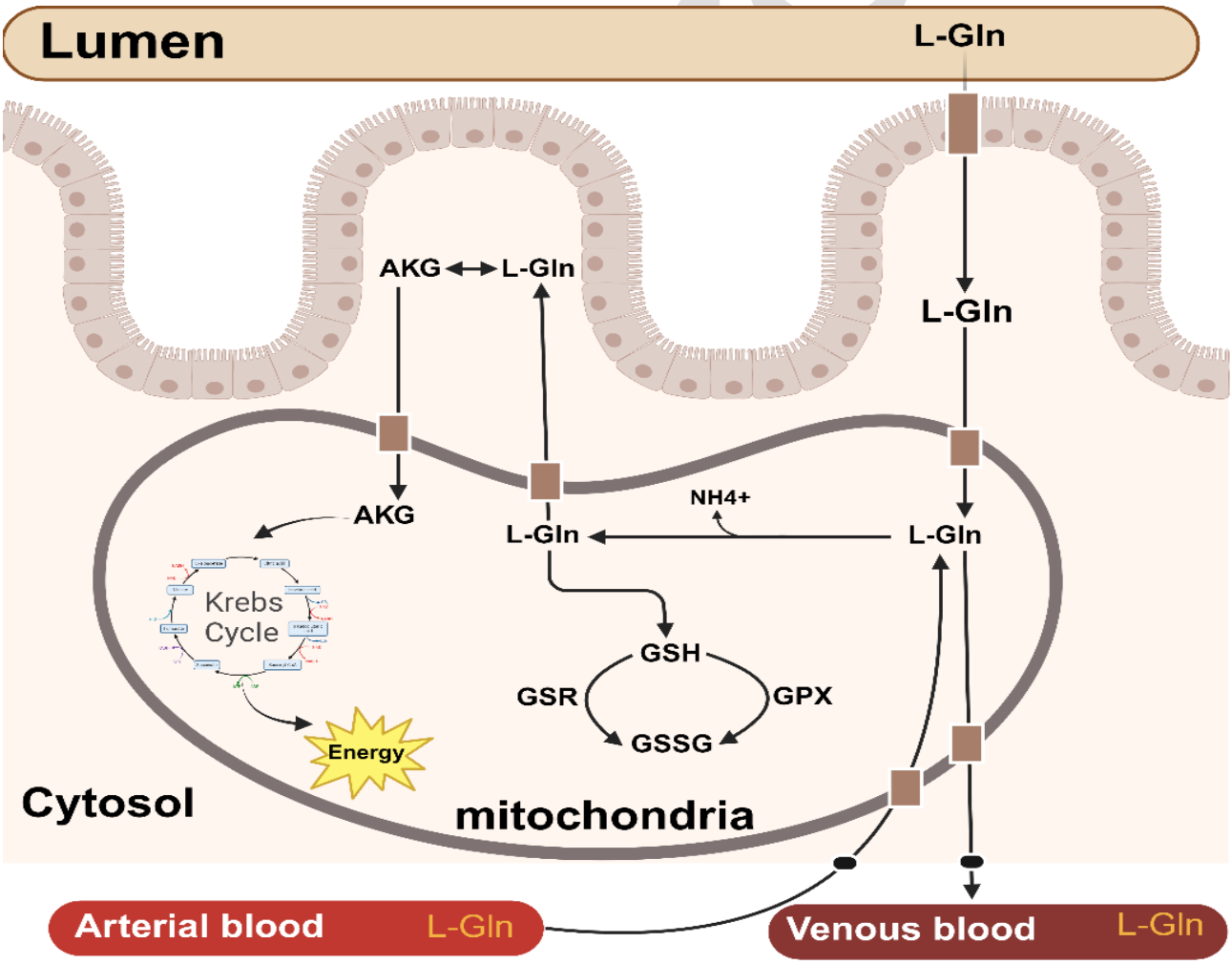

Fig. 2: Graphic representation of glutamine catabolism in enterocytes.

Glutamine is taken up from the intestinal lumen and arterial blood by enterocytes. Within the cell, it is metabolized in the mitochondria to produce alpha-ketoglutarate, which enters into the Krebs cycle to produce energy (ATP), ammonia (NH_3), and other intermediates. This process highlights the role of the small intestine as a major site of glutamine utilization, supporting its own energy needs and metabolic functions. Adapted from Curi *et al*., 2016. Abbreviations: AKG, alpha-ketoglutarate; L-Gln, L-Glutamine; GLUase, glutaminase; GSR, glutathione reductase; GSK, glutathione synthetase; GSSG, oxidized glutathione.

The role of Glutamine in monogastric animal's performance: In the initial phase of a pig's growth, their digestive system may not absorb or fully process nutrients due to underdeveloped intestines, potentially leading to malnutrition. Furthermore, their sensitive intestines can be adversely affected by external harmful factors, causing stress and damage. Consequently, it is vital to meticulously control the piglets' diet and medication during this stage to protect their intestinal health (Xing *et al*., 2017). One of the essential amino acids, glutamine (Glu), is found in the higher concentration in the blood and milk of mammals. It plays a crucial role in providing carbon for purine and pyrimidine synthesis. Additionally, it aids in Krebs cycle by generating α-ketoglutaric acid via deamination and transamination processes (Wu, 2010). Moreover, glutamine significantly promotes the growth and repair of intestinal epithelial cells. During periods of stress in piglets, the natural glutamine produced by the body may not be sufficient, necessitating the supplementation of glutamine in their diet (Zhang *et al*., 2016). Yi *et al.* (2001) have indicated that including 1% Glu in the feed resulted in enhanced weight gain and feed efficiency ratio (FCR) for turkey poults in the 1st week after hatching in comparison to poults being fed a standard corn soya bean meal (SBM) diet. Moreover, the study reported that adding 1% Glu to feed also led to improved feed efficiency in piglets (Kitt *et al*., 2002). Moreover, supplementing with glutamine enlarged the intestinal villi in young turkeys and newly weaned pigs (Yi *et al*., 2005). It was depicted that glutamine enriched diet stimulates the proliferation of the gut mucosa in rats. Additionally, incorporating 1.5% glutamine into total parenteral nutrition diets plays a central role in preserving gut integrity, thereby serving as a significant factor in the prevention of bacterial infections (Naka *et al*., 1996). Glutamine is widely used as a clinical nutrition supplementation for patients before and after surgeries. It is also popular among elite athletes to support the restoration of immune functions (Cruzat *et al*., 2018). The NAFLD (Nonalcoholic fatty liver disease) is a prevalent and long-lasting liver condition that encompasses a variety of liver dysfunctions. These may include isolated hepatic steatosis, nonalcoholic steatohepatitis (NASH), and other liver-related disorders (Yu *et al*., 2021). NASH (nonalcoholic steatohepatitis) is a form of NAFLD that is identified by liver cell enlargement, inflammation, oxidative stress, and different levels of liver scarring. If left untreated, NASH can advance to cirrhosis and even hepatocellular carcinoma, a type of liver cancer (Zhang *et al*., 2021). Alanyl-glutamine (Ala-Glu) is a valuable nutrient known for its ability to promote gut health and its wide-ranging therapeutic effects in combatting diseases associated with inflammation and oxidative stress. Ala-Glu acts to reduce oxidative stress by enhancing the activities of important enzymatic antioxidants like superoxide dismutase (SOD) and glutathione peroxidase (GPX), thereby mitigating lipid accumulation. Moreover, it aids in inflammation improvement by reducing active macrophages and proinflammatory mediators and exhibits potential to inhibit the severity of liver fibrosis by targeting hepatic stellate cell activation. Ala-Glu treatment decisively shows potential in managing NASH (de Oliveira Santos *et al*., 2021, Hu *et al*., 2022). Glu is the main energy source for enterocytes, colonocytes, lymphocytes, and macrophages in the body. It used as a building block for the nucleotide synthesis and act significantly in the glutathione production, an important antioxidant known for its potential protective effects in a wide range of circumstances (Wischmeyer, 2008). Glutamine is an important source of energy for the intestine's cells lining known as enterocytes. It acts positively in reducing the movement of harmful bacteria across the intestinal barrier, which can help in lowering the risk of developing sepsis. In cases of sepsis and endotoxemia, there may be a noticeable decrease in the intestinal ability to effectively consume glutamine, which can further exacerbate the condition (Melis *et al*., 2004, Singleton *et al*., 2005). Recent researches have highlighted the potential depletion of glutamine stores, despite their significant reserves, particularly during catabolic slurs such as trauma, infection, fasting, and acidosis. This is mainly essential for the individuals who are particularly vulnerable, such as the elderly, patients recovering from surgery, individuals with sepsis, those battling cancer, and very low birth weight (VLBW) toddlers. These individuals often experience high levels of stress, have limited energy and protein resources, and may be undergoing treatment involving catabolic glucocorticoids (Xian-li *et al*., 2004, Çekmen *et al*., 2011).

Previously, it was found that adding 10 grams per kilogram of Glu to the diet resulted in improved weight gain, higher intestinal villi and concentrations of serum immunoglobulin A and G in broiler chicks from 21 days post-hatch when compared to diets without supplementation (Bartell and Batal, 2007). This research hypothesized that supplementing broiler chickens with 10 g/kg of Glu may have a protective effect. It is suggested that this supplementation could help to maintain growth performance, gut health and morphology, serum biochemical indicators, and offset metabolic losses caused by infection (Xue *et al*., 2018).

Glutamine supplements have been proven with multiple benefits. It helps improve nitrogen balance, which is essential for bodily functions. Additionally, it enhances the rate of protein synthesis, which is crucial for muscle repair and growth. Glu act significantly in maintaining immune cells and mucosal cells integrity and structural and lining of the digestive and respiratory systems. Furthermore, it is believed to prevent the movement of bacteria and toxins from the intestinal tract to the general circulation, thereby contributes to the overall gut health (Mitsuhashi, 2014). It is an essential nutrient for the gastrointestinal tract, acts as a major source of energy for enterocytes and has been observed in protection against damage to the intestinal epithelial cells in weaned pigs

(Ueno *et al*., 2011). An important consideration when using Glu as a dietary supplement is its tendency to become unstable when in solution or stored for long periods. This leads to the production of toxic byproducts, which is a significant limitation (Carneiro-Filho *et al*., 2003). Glutamine is crucial in supporting various metabolic processes within the body. It serves as a key intermediator in energy metabolism and a building block for peptides and non-peptides synthesis. These non-peptides include essential components such as nucleotide bases, glutathione, and neurotransmitters (Coster *et al*., 2004). Its addition to the diet can potentially enhance the intestinal environment, resulting in improved absorption of nutrients. Numerous studies have extensively documented the positive effect of Glu on the broiler's performance across diverse conditions and environments (Nassiri Moghaddam and Alizadeh-Ghamsari, 2013). The presence of free AA in intestine lumen triggers the amino acid transport system (Diamond & Karasov, 1987) and pancreatic proteases secretion (Johnson, 2001). Hence, amino acids in intestinal lumen can boosts the absorption capacity (Maiorka *et al*., 2000). It was observed that when 1% glutamine (Glu) was added to diet, it showed a significant effect on the development of the intestinal structure in young chickens. Specifically, it led to improvements in the villi height (VH), crypt depth (CD), and villus to crypt ratio (VCR) in the duodenum, as well as the VH in the ileum at 7 days. Moreover, the continuous supplementation enhanced the overall intestinal structure, including VH, CD, and VCR, until the chickens reached 14 days of age. Furthermore, the study highlighted the beneficial influence of both 1% and 1.5% Glu supplements in the diet, which resulted in increased VH and villus surface area in the duodenum and jejunum of 21 and 42-day-old broilers (Nassiri Moghaddam and Alizadeh-Ghamsari, 2013). It was also shown that the efficient use of Glu by the intestinal mucosal cells of channel catfish showed an enhancement of the intestinal villi (Pohlenz *et al*., 2012).

Despite the lack of improved growth performance at the end of experiment, it was observed that the supplemented Glu and Arg showed a significant impact on the morphological indicators and likely enhanced nutrient absorption in the digestive tract of hybrid striped bass (Cheng *et al*., 2012). It was depicted that diets supplemented with Glu not only improved the overall performance of neonate broiler chickens but also contributed to the enhanced development of their intestinal mucosa (Alajaji, 2024). This enhancement was characterized by longer villi and higher villus: crypt ratio (VCR), which, in turn, facilitated increased absorption area for nutrients. Consequently, this could potentially impact the digestibility values of amino acids (Namroud *et al*., 2017). Manvailer (2013) indicated that the optimal L-Glu supplementation approach involved providing 1.0% of L-Glu until 14 days of age, followed by 0.5% of L-Glu until 21 days, and then stopping supplementation from 22 to 42 days of age. This regimen resulted in significant improvements in body weight gain, carcass weight, breast weight, and breast meat yield (Manvailer, 2013). It has been observed that glutamine in diet leads to an increase villi height in the jejunum and the mucosal muscle layer thickness. This supplementation also prevents the reduction of villus width and crypt depth. The findings suggest that the utilization of nutrients from feed is closely linked to the health of the intestinal structure and villi. Furthermore, intestine serves as a primary site for the dietary nutrients absorption and consumption, but maintaining the health of the villi is important for efficient nutrient uptake (Pluske *et al*., 1996). The structure of the villi in small intestine plays a great role in nutrient absorption. Longer villi create a larger surface area, which enhances the absorption capacity for available nutrients (Rashid *et al.,* 2023). This, in turn, contributes to improved performance, particularly during the early stages of a chick's life (Caspary, 1992). Furthermore, by utilizing Glu as a substrate of gut cells, the essential enzymes such as maltase and sucrase can be enhanced. This improvement can lead to better breakdown and absorption of nutrients, potentially resulting in accelerated broiler growth (Sakamoto *et al*., 2011, Ribeiro Júnior *et al*., 2015). Jing Ge *et al*. (2009) noted an enhancement in the levels of superoxide dismutase and GSH-Px, which led to an improved antioxidant activity of broilers that were fed with 0.5% L-Glu diets (Dong JinGe *et al*., 2009).

Glu acts as a substrate for the development of lymphocytes and macrophages, which mainly constitute the body's immune system. Furthermore, it enhances the activity of various immune cells, including promoting T-cell proliferation, stimulating cytokine production, aiding in B-lymphocyte differentiation, facilitating antigen production, and supporting macrophage phagocytosis. Results of In-vivo studies provide strong evidence that supplementing Glu leads to noticeable enhancements in immune system functionality. Soltan (2009) depicted that broilers that were fed with 1% Glu containing diet, exhibited significantly higher red blood cells, platelets, and hemoglobin percentage compared to broilers that were fed a diet without Glu (Soltan, 2009). In response to pathogens, there was an increase in enzyme glutaminase activity, that is involved in the process of Glu deamination, observed across all lymphoid organs including spleen, thymus and lymph nodes (Yamauchi, 2002). Barter and Batal, (2007) observed that 1% Glu in diet, improved relative weight of both the thymus and spleen compared to the group that was fed with control diet (Bartell and Batal, 2007). Similarly, a study conducted on 7-day-old broilers revealed that when their diet included 1% Glu, it resulted only in spleen weight enhancement. Conversely, the relative weight of other lymphoid organs remained consistent across all treatment groups (Sakamoto *et al*., 2011).

Glutamine's role in poultry nutrition: Glutamine, traditionally classified as a non-essential amino acid, has emerged as a critical nutrient in poultry nutrition, particularly under stress, rapid growth, or disease challenges. Its multifaceted roles span gut health, immune modulation, metabolic regulation, and disease resistance, positioning it as a cornerstone of modern poultry dietary strategies. Recent advances in poultry-specific research highlight glutamine's indispensable contributions to optimizing productivity, health, and resilience in commercial and backyard flocks alike (Zhang *et al.* 2016).

Glutamine enhances growth performance and protein metabolism: Glutamine plays a pivotal role in protein synthesis and muscle development in poultry. A landmark

study on yellow-feathered broilers demonstrated that dietary supplementation with 0.6–1.0% glutamine significantly improved average daily weight gain (ADG) by 8.8–11.9% across different growth phases (1–49 days) (Xue *et al.* 2018). Notably, serum uric acid levels, a marker of protein catabolism, decreased by 40.6–45.6% in birds receiving 0.8–1.0% glutamine, indicating enhanced nitrogen utilization efficiency and reduced metabolic waste. These findings align with broader research showing that glutamine activates the mTORC1 pathway in skeletal muscle, stimulating ribosomal S6 kinase (S6K1) phosphorylation and increasing lean mass accretion by 18% (Wu *et al.* 2021). Conversely, glutamine deficiency elevates proteolysis markers (*MAFbx*, *MuRF1*), exacerbating muscle wasting during catabolic states such as heat stress or infection.

Recent innovations in precision nutrition emphasize glutamine's synergy with branched-chain amino acids (BCAAs). A 2025 study using a Box-Behnken design revealed that optimizing BCAA-to-glutamine ratios (e.g., 20% BCAA with 1% glutamine in 17% crude protein diets) maximized breast meat yield while minimizing abdominal fat deposition. This highlights glutamine's dual role in promoting muscle growth and regulating lipid metabolism, offering a strategy to balance productivity and carcass quality in low-protein diets (Berres *et al.* 2010, Qaid and Al-Garadi 2021).

Glutamine as a guardian of gut health and barrier function: The gastrointestinal tract is a primary site of glutamine utilization in poultry, where it serves as the chief energy source for enterocytes—cells critical for nutrient absorption and mucosal integrity. Research shows that 1% dietary glutamine supplementation increases duodenal villus height by 18% and villus-to-crypt ratio (VCR) by 22% in 14-day-old broilers, directly correlating with improved feed conversion ratios (Dai *et al.* 2009). These morphological improvements are attributed to glutamine's ability to stimulate enterocyte proliferation, suppress apoptosis, and enhance mucin-2 secretion, which fortifies the intestinal barrier against pathogens like *Salmonella* and *Clostridium perfringens* (Nazir *et al.* 2024a)

Fermented feeds, enriched with glutamine through lactic acid bacteria, further amplify these benefits. Studies demonstrate that lacto-fermentation reduces phytic acid and anti-nutrients in grains, increasing vitamin B bioavailability (e.g., riboflavin, niacin) and fostering a gut microbiome dominated by *Lactobacillus* while suppressing *E. coli* by 30–40%. This prebiotic effect synergizes glutamine's role in maintaining gut integrity, as evidenced by reduced necrotic enteritis lesions (40%) in *C. perfringens*-challenged broilers fed 1.2% glutamine 6. Such outcomes underscore the potential of combining glutamine with fermented feeds to enhance nutrient utilization and disease resistance (Nazir *et al.* 2024a).

Immunomodulatory and antioxidant properties: Glutamine is indispensable for immune cell function, fueling lymphocytes, macrophages, and neutrophils during pathogen challenges. Broilers supplemented with 1.2% glutamine exhibit 35% higher serum IgA levels, enhancing mucosal immunity and reducing systemic inflammation (Nazir *et al.* 2024b). Mechanistically, glutamine inhibits the NF-κB pathway, halving pro-inflammatory cytokines like TNF-α and IL-6 in lipopolysaccharide (LPS)-challenged macrophages. This anti-inflammatory action is critical in intensively reared poultry, where chronic inflammation from overcrowding or pathogens impairs growth and feed efficiency (Kuo *et al.* 2024).

As a precursor for glutathione (GSH), glutamine bolsters antioxidant defenses (Yan *et al.,* 2024). In heat-stressed broilers, 0.8% dietary glutamine elevates hepatic GSH levels by 25%, reducing lipid peroxidation markers like malondialdehyde (MDA) and improving survival rates (Kuo *et al.* 2024). This antioxidant capacity is particularly vital during aflatoxin B1 exposure, where glutamine supplementation preserves liver function by mitigating oxidative damage (Nazir *et al.* 2024b).

For more critical synthesis, Table 1 provides a comparative analysis of glutamine supplementation studies across different species, experimental conditions, and dosages. A critical examination reveals that the effectiveness of glutamine is highly context-dependent. Consistent benefits for gut morphology are observed during critical developmental or stress periods (e.g., post-hatch in poultry, post-weaning in piglets). However, the translation of these morphological improvements into enhanced growth performance is not universal, as seen in fish studies. Furthermore, the form of supplementation (free glutamine vs. stable dipeptides like alanyl-glutamine) and the dosing strategy (constant vs. phased) emerge as critical factors influencing outcomes, potentially explaining inconsistencies across literature. This analysis underscores the importance of adapting glutamine supplementation protocols to specific species, physiological states, and challenges to achieve optimal results.

Glutamine: a key player in disease resistance: Glu, usually considered as non-essential amino acid, is believed to become important during severe infections, mainly when the gut mucosal barrier is compromised. This means that in certain conditions, the body may require higher levels of glutamine to support immune function and maintain gut health (Souba *et al*., 1990). It plays a vital role as a primary metabolite and energy resource that nourishes enterocytes. It significantly maintains the structure of the mucosal lining by synthesizing mucin, which is crucial for protecting the intestinal barrier in response to bacterial damages (Lacey and Wilmore, 1990, Khan *et al*., 1999). Supplementing with glutamine supports the repair of damaged intestinal mucosa and promotes the differentiation of enterocytes, which are significant cells in intestine aid in nutrient absorption (Murakami *et al*., 2007). Glutamine, a vital amino acid, is present in abundance within the body. Several studies depicted its essential role in supporting the glutathione (GSH)-mediated antioxidant defense, highlighting the significance of its availability (Newsholme *et al*., 2011). L-glu is essential for triggering the heat shock protein (HSP) response by engaging heat shock factor 1 (HSF-1). This process plays main role in cellular protection and stress adaptation (Xue *et al*., 2012). Heat shock proteins (HSPs) form a group of polypeptides that combine unfolded or denatured proteins due to stress-induced conditions. These proteins are essential for maintaining proper protein function and preventing cellular damage

during stressful situations (Heck *et al*., 2011). In catabolic conditions, such as intense aerobic exercise, infection, and acute inflammation, the body's demand for glutamine surpasses its supply, leading to a systemic deficiency (Fig. 3). This deficit can impair critical recovery pathways and immune function. In efforts to counteract this deficiency,

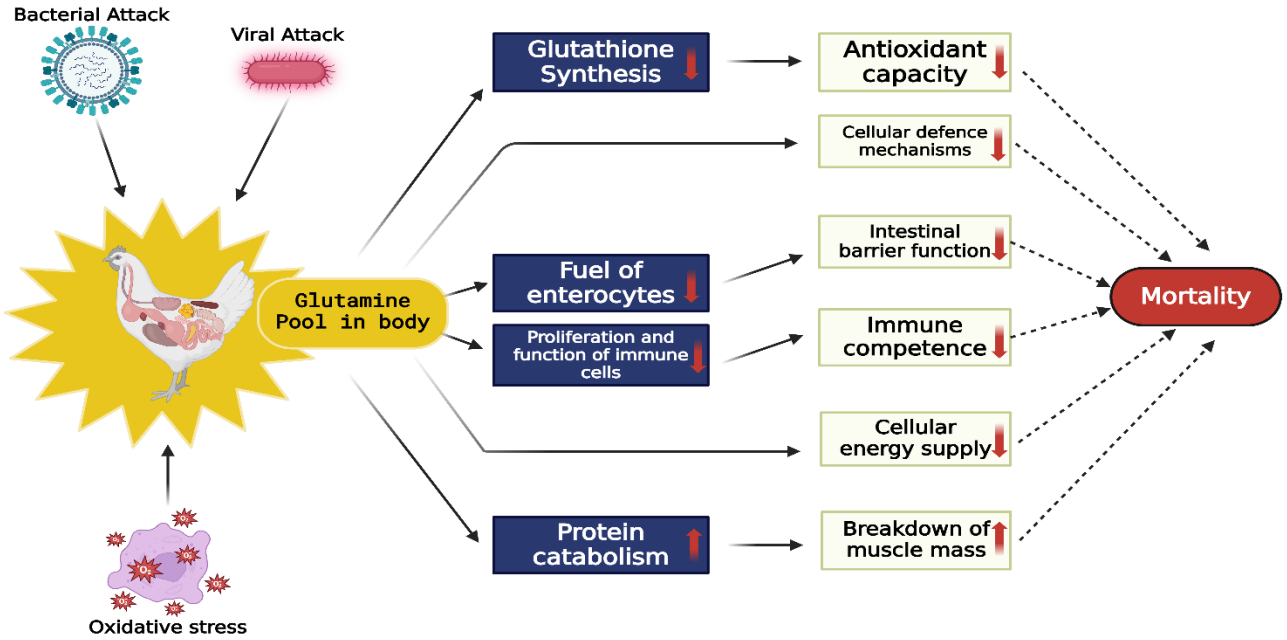

Fig. 3: Consequences of glutamine depletion during metabolic stress.

Table 1: Critical analysis of glutamine supplementation across species, conditions, and experimental designs

Species	Stress Condition	Dosage	Key Findings	Critical Analysis	Reference
Broiler Chickens	Standard conditions (Starter phase)	1.0% L-Glutamine	↑ Villus height, crypt depth, VH:CD ratio in duodenum/ileum at 7 days.	Benefits are most pronounced in early growth. Effect diminishes with age, suggesting a developmental window of efficacy.	(Nassiri Moghaddam and Alizadeh-Ghamsari, 2013)
Broiler Chickens	Standard conditions (Entire cycle)	1.0% until d14, 0.5% until d21, then 0%	↑ Body weight gain, carcass weight, breast meat yield.	Phased supplementation was optimal. This challenge suggests use of a constant dosage, indicating that requirements change with intestinal maturation and growth rate.	(Manvailer, 2013)
Broiler Chickens	Necrotic Enteritis challenge	1.0% L-Glutamine	Maintained growth performance, improved gut morphology, and serum biochemistry.	Demonstrates therapeutic potential during disease. The benefit is not just prophylactic but also aids in recovery, a key distinction from studies in healthy birds.	(Xue et al., 2018)
Broiler Chickens	Heat Stress	0.5% L-Glutamine	↑ Antioxidant capacity (SOD, GSH-Px).	Focused on oxidative status, not growth. Highlights a key mechanism (antioxidant defense) that may underpin benefits seen in other stress models.	(Dong et al., 2009)
Turkey Poults	Standard conditions (Post-hatch)	1.0% L-Glutamine	↑ Weight gain, Feed Efficiency, intestinal villi height.	Early post-hatch period is universally a vulnerable phase across poultry where glutamine shows consistent benefits for gut development.	(Yi et al., 2005)
Weaned Piglets	Weaning Stress	1.0% L-Glutamine	↑ Villus height, improved feed efficiency.	Weaning stress in piglets is analogous to post-hatch stress in poultry. Glutamine's role in preserving gut integrity during barrier challenges is consistent across monogastrics.	(Kitt et al., 2002)
Weaned Piglets	Weaning Stress / Undernutrition	Alanyl-Glutamine (Ala-Gln) dipeptide	Promoted intestinal epithelial cell homeostasis in vitro and in vivo.	Use of a stable dipeptide. Suggests that the form of supplementation is critical, especially for unstable molecules like glutamine, potentially explaining variable results in earlier studies using free glutamine.	(Ueno et al., 2011)
Hybrid Striped Bass	Standard conditions	2% Glutamine + 1% Arginine	↑ Intestinal villi; No improvement in final growth performance.	A critical example of detach between morphology and performance. Improved gut structure did not translate to growth, possibly due to species-specific metabolism or suboptimal diet formulation.	(Cheng et al., 2012)
Rodent Model (Mice/Rats)	NASH / Steatohepatitis	Alanyl-Glutamine (Ala-Gln)	↓ Oxidative stress, inflammation, and liver fibrosis.	Uses a specific disease model to elucidate mechanisms (antioxidant, anti-inflammatory). Provides a mechanistic basis for benefits that are harder to measure directly in production animals.	(Hu et al., 2022; de Oliveira Santos et al., 2021)
Rodent Model (Rats)	Prolonged Exercise	Free Glutamine vs. Ala-Gln dipeptide	Both forms improved muscle damage and inflammation markers, with dipeptides often showing superior bioavailability.	Directly compares supplementation forms. Highlights a major confounding variable in the literature: the instability of free glutamine may lead to underestimation of its effectiveness in some studies.	(Cruzat et al., 2010)
Broiler Chickens	Transportation Stress	1% L-Glutamine	Modulated blood parameters; variable effects on performance.	Effects are context-dependent. The type and severity of stressor (physical vs. pathogenic) influence the outcome, suggesting glutamine is not a universal "silver bullet."	(Shakeri et al., 2016)

numerous studies have explored the use of dietary L-glutamine supplements, showing varied outcomes (Bassini-Cameron *et al*., 2007). L-Glu, classified as a nonessential amino acid from a nutritional perspective, is the most plentiful free amino acid found in the human body. It is predominantly formed and released into the bloodstream by the actively contracting skeletal muscles (Newsholme *et al*., 2003). However, in high-intensity or prolonged strenuous exercises can create a catabolic state in the body, causing a reduction in the L-glutamine pool (Cruzat and Tirapegui, 2009). This response means that certain substances indicating muscle damage are being released into the plasma (Cruzat *et al*., 2010), mostly because of over-production of reactive nitrogen and oxygen species (RNS/ROS) (Finaud *et al*., 2006). Under such conditions, the organism encounters a state of oxidative damage, characterized by an elevated overall oxidant potential. To protect the cells from reactive oxygen species (ROS) and reactive nitrogen species (RNS), the tripeptide GSH (L-γ-glutamyl-L-cysteinylglycine) serves as a crucial non-enzymatic soluble intracellular antioxidant. Its functions extend to offering protection and supporting various metabolic processes in cellular metabolism, such as mitigation of oxidative stress (Roth, 2008).

Nuclear transcription factor-kappa B (NF-κB) acts as a signaling molecule that orchestrates the regulation of a wide array of genes. These genes take part in modulation of immune and stress responses, regulating inflammatory processes, and safeguarding against apoptosis, or programmed cell death (Smahi *et al*., 2002). According to some research, Glu has the potential to prevent the activation of NF-κB, a key regulator of inflammatory responses. This inhibition may lead to a decrease in the release of inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukins (ILs), ultimately resulting in a reduction in inflammation (da Silva Lima *et al*., 2013, Hou *et al*., 2012).

Glutamine is a vital compound known for its ability to scavenge free radicals in enterocyte and lymphocyte cells. It is commonly listed as an essential "immune-nutrient" (Xi *et al*., 2012). Numerous studies involving animals and clinical research have provided strong evidence that glutamine plays a significant role in maintaining the optimal function and health of the intestinal mucosa. Furthermore, it has been observed to offer protective effects against various stressors, such as the attack of pathogenic organisms, infections, and immunological challenges, in controlled laboratory environments and within living organisms as well (Rao *et al*., 2000). For instance, the glutamine has been observed in protein production in enterocytes, support the growth and maturation of the intestinal tract, control the expression of tight junction proteins and intestinal immunity, restore the function of the gut barrier, and prevent cell death or shrinkage caused by stress or infection (Wijtten *et al*., 2011).

During catabolic states (e.g., illness, trauma), the body's consumption of glutamine surpasses its endogenous production. This deficit creates a shortage of glutamine for critical anabolic and immune-supporting pathways, impairing recovery. Without exogenous supplementation, this deficiency can lead to adverse outcomes, including an increased risk of sepsis, multiple organ failure, and mortality.

Animal studies have provided multiple pieces of evidence indicating that the positive impacts of Glu on integrity of the intestinal mucosa and normal functioning of the immune system are largely dependent on its concentration in the bloodstream (Shakerı *et al*., 2016). The reason is glutamine plays a role in the activation of mast cells, the production of adrenal cortisol and corticotrophin-releasing factor, and the release of various mediators such as histamines, cytokines, proteoglycans, and proteases. Additionally, it helps improve the function of the mucosal barrier (Wu *et al*., 2011). Moreover, the anti-apoptotic effects are caused by the apoptotic pathway mediated through the mitochondria or death receptors (Matés *et al*., 2006). Further, Bartel and Batal (2007) that broiler chickens that were given Glu showed increased levels of IgA (immunoglobulin A) in their serum, bile, and intestine. IgA serves as a protective barrier against bacterial attachment to mucosal cells. Therefore, incorporating Glu into the chickens' diet appeared to stimulate the production of IgA, thereby enhancing their immunity against bacterial and parasitic antigens (Bartell and Batal, 2007).

Conclusions: Glutamine is a conditionally essential amino acid that plays a crucial role in various physiological processes. Its significance becomes particularly apparent during disease states, as it supports immune function, maintains intestinal integrity, and promotes tissue repair. Supplementing with exogenous glutamine can be beneficial in alleviating the adverse effects of glutamine deficiency and improving overall outcomes in animals suffering from illness or injury.

Future directions and practical implications: While glutamine's benefits are well-documented, challenges remain in optimizing its use. Breed-specific responses, particularly in heritage or slow-growing lines, require investigation. Additionally, interactions with emerging feed additives like phytogenic or symbiotic warrant exploration. For instance, combining glutamine with inulin a prebiotic shown to enhance early chick growth via maternal fecal microbiota transplantation could amplify gut health benefits.

Economically, glutamine supplementation offers a sustainable alternative to antibiotic growth promoters (AGPs). However, cost-benefit analyses must consider fluctuating raw material prices and regional feed formulation practices.

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