World Journal of Applied Research
worldappliedjournal.com
Online ISSN: 3107-8885
Received: 30-01-2026, Accepted: 28-02-2026, Published: 16-03-2026
Volume 2, Issue 1, 2026, Page No. 59-62

The role of immunonutrition in modulating immune responses and inflammation: A comprehensive review

Saswati Sanyal[1], Ishita Bhowmick[2], Sneha Thakur[3], Shweta Parida[4*]
[1] Department of Food and Nutrition, Swami Vivekananda University, Barrackpore, West Bengal, India
[2] Clinical Dietician, Dr Datta's Clinic, Chandanagar, West Bengal, India
[3] Department of Dietetics and Applied Nutrition, Amity University, Kolkata, West Bengal, India
[4] Assistant Professor and Head, Department of Food Science and Technology, School of CIST, KISS-DU, Bhubaneswar, Odisha, India
Corresponding Author: Shweta Parida

Abstract
Immunonutrition (IN) is an emerging paradigm in nutritional science that involves the administration of specific nutrients to modulate inflammatory, metabolic, and immune responses. Unlike conventional nutritional support, which primarily aims to maintain energy balance and preserve lean body mass, immunonutrition employs bioactive substrates such as omega-3 fatty acids, glutamine, arginine, nucleotides, and selected micronutrients as therapeutic agents to enhance immune competence and improve clinical outcomes. These nutrients exert beneficial effects by maintaining intestinal mucosal barrier integrity, supporting immune cell proliferation and function, regulating gene expression, reducing oxidative stress, and attenuating excessive inflammatory responses, including cytokine storms. Growing evidence suggests that immunonutrition may reduce infectious complications, shorten hospital stay, improve wound healing, and enhance recovery in critically ill patients, individuals undergoing major surgery, and those with severe viral infections. However, clinical outcomes remain inconsistent due to variations in patient populations, timing of intervention, nutrient composition, and dosing strategies. This review summarizes the biochemical mechanisms underlying key immunonutrients, critically evaluates current clinical evidence across critical care, surgical oncology, and infectious diseases, and discusses the limitations, challenges, and future prospects of personalized immunonutrition in precision medicine.

Keywords: Immunonutrition, glutamine, arginine, Omega-3 fatty acids, nucleotides, immune modulation, inflammation, critical care, surgical nutrition, precision nutrition

Introduction

The bidirectional relationship between nutrition and immunity is well-established; malnutrition impairs immune function, while immune activation alters metabolic demands (Méndez López *et al*., 2024; Venter *et al*., 2020) [7]. Immunonutrition represents a shift from passive nutritional support to active metabolic and immunological modulation (Calder, 2007) [1]. By delivering specific nutrients at doses higher than standard dietary requirements, IN seeks to upregulate host defenses without exacerbating systemic inflammation (Ham & Kim, 2025; Perez Arteaga, 2026) [3, 5]. In clinical settings such as major abdominal surgery, severe burns, trauma, and acute respiratory distress syndrome (ARDS), the body enters a state of hyper-inflammation coupled with profound immunosuppression (Calder, 2007; Tan *et al*., 2014) [1, 6]. Standard enteral formulas often fail to address these specific metabolic shifts (Perez Arteaga, 2026) [5]. Consequently, tailored immunonutrient formulations are increasingly evaluated for their capacity to reduce infectious complications, hospital length of stay (LOS), and mechanical ventilation duration (Dushianthan *et al*., 2019; Ham & Kim, 2025) [2, 3].

Key Bioactive Immunonutrients and Mechanisms of Action

Bioactive immunonutrients represent a specialized class of nutritional substrates engineered to actively modulate immune competence, tissue repair, and metabolic inflammation during periods of severe physiological stress (Sengupta, 2025) [11]. Within this metabolic paradigm, glutamine shifts from a non-essential status to a conditionally essential amino acid, serving as the obligate fuel source for enterocytes and rapidly proliferating lymphocytes while preserving critical intestinal tight junction architecture (Wernerman, 2014) [12]. Concurrently, arginine functions as the principal substrate for nitric oxide synthesis—essential for microvascular perfusion and macrophage bactericidal pathways—while directly upregulating the CD3 zeta chain expression necessary for adaptive T-cell receptor signaling and clonal expansion (Barbul, 2008) [8]. To counterbalance systemic hyper-inflammation, omega-3 polyunsaturated fatty acids structurally displace arachidonic acid within leukocyte cell membranes, competitively diminishing the cascade of pro-inflammatory eicosanoids and instead prompting the synthesis of specialized pro-resolving mediators that actively halt cellular inflammatory injury (Calder, 2017) [9]. Finally, exogenous nucleotides provide the critical purine and pyrimidine building blocks required to satisfy the intensive nucleic acid synthesis demands of expanding immune cell populations and mucosal structures, which frequently exceed endogenous salvage pathway capacities during critical illness (Schneider & Atkinson, 2000) [10].

1. Glutamine

Glutamine is the most abundant free amino acid in the human body and is normally classified as a non-essential amino acid because it can be synthesized endogenously.

However, during conditions of severe physiological stress such as critical illness, trauma, sepsis, burns, or major surgery, the body's demand for glutamine exceeds its production, making it a conditionally essential amino acid. Glutamine serves as the primary energy substrate for rapidly proliferating cells, including enterocytes, lymphocytes, and macrophages, through the process of glutaminolysis, thereby supporting intestinal health and immune cell function. It also plays a vital role in maintaining the integrity of the intestinal mucosal barrier by preserving tight junction proteins such as occludin and zonula occludens-1, which help prevent bacterial translocation and systemic infections. Furthermore, glutamine is a key precursor for the synthesis of glutathione (GSH), the body's principal intracellular antioxidant, which protects immune cells from oxidative stress, reduces inflammation, and enhances overall immune defense. Through these mechanisms, glutamine contributes significantly to immune regulation, gastrointestinal health, and recovery during critical illness.

2. Arginine

Arginine is a conditionally essential amino acid that plays a concentration-dependent role in immune regulation and vascular function, particularly during critical illness (Poeze *et al*., 2011) [15]. It is essential for the expression of the CD247 ($CD3\zeta$) chain of the T-cell receptor, which is necessary for T-cell proliferation, cell-cycle progression, and effective adaptive immune responses (García-Navas *et al*., 2012; Rodriguez *et al*., 2006) [13, 16]. In addition, arginine serves as the exclusive substrate for nitric oxide synthase (NOS) isoforms, the enzymes responsible for the production of nitric oxide (NO) (Víteček *et al*., 2012). Nitric oxide generated by activated macrophages possesses potent antimicrobial activity and contributes to the elimination of invading pathogens while also regulating vascular tone and blood flow (Poeze *et al*., 2011) [15]. However, the clinical use of arginine requires careful consideration, especially in patients with severe, uncompensated sepsis. Excessive arginine supplementation may overstimulate inducible nitric oxide synthase ($iNOS$), resulting in toxic levels of NO production, profound vasodilation, systemic hypotension, and subsequent hemodynamic instability (Nicholls *et al*., 2007; Suchner *et al*., 2002) [14, 17]. Therefore, although arginine offers important immunomodulatory and wound-healing benefits, its supplementation should be strictly individualized according to the patient's clinical and metabolic condition (Suchner *et al*.,

3. Omega-3 Polyunsaturated Fatty Acids (ω-3 PUFAs)

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids that play a significant role in modulating inflammatory and immune responses. These fatty acids become incorporated into cell membrane phospholipids, where they partially replace arachidonic acid (AA), thereby altering the synthesis of inflammatory mediators. Upon immune cell activation, EPA and DHA are metabolized into less inflammatory eicosanoids, including 3-series prostaglandins and 5-series leukotrienes, instead of the highly pro-inflammatory 2-series prostaglandins and 4-series leukotrienes derived from ω-6 fatty acids. In addition, ω-3 PUFAs serve as precursors for specialized pro-resolving mediators (SPMs), such as resolvins, protectins, and maresins, which actively terminate inflammation, enhance the clearance of inflammatory cells, and promote tissue repair and healing. Furthermore, EPA and DHA inhibit the activation of the nuclear transcription factor nuclear factor-kappa B (NF-κB), resulting in reduced expression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). Through these mechanisms, ω-3 PUFAs help regulate excessive inflammation, improve immune homeostasis, and support recovery in inflammatory and critical illness conditions.

4. Nucleotides

Nucleotides are essential biomolecules that serve as the building blocks of DNA and RNA and play a crucial role in cellular metabolism, energy transfer, and immune function. During conditions of rapid cell proliferation, such as critical illness, infection, trauma, or surgery, activated lymphocytes, enterocytes, and other rapidly dividing cells require large amounts of purine and pyrimidine nucleotides to support DNA synthesis and cellular replication. Although the body can synthesize nucleotides through *de novo* synthesis and salvage pathways, these mechanisms may become inadequate during hypermetabolic and catabolic states, leading to an increased dependence on dietary nucleotide sources. Adequate nucleotide availability supports the proliferation and function of immune cells, maintains intestinal mucosal integrity, and enhances tissue repair. Conversely, dietary nucleotide restriction has been associated with impaired T-cell-mediated immune responses, reduced lymphocyte proliferation, and decreased natural killer (NK) cell activity, thereby compromising host defense against infections. Therefore, nucleotide supplementation may provide immunological and gastrointestinal benefits, particularly in critically ill patients with increased metabolic demands.

Clinical Applications of Immunonutrition

1. Perioperative Care in Surgical Oncology

Major gastrointestinal oncology surgeries induce significant metabolic stress and immunosuppression, predisposing patients to postoperative infections. Current Enhanced Recovery After Surgery (ERAS) guidelines strongly consider perioperative enteral immunonutrition (combining arginine, omega-3, and nucleotides) for 5 to 7 days prior to major upper GI surgery, regardless of baseline nutritional status. Clinical trials demonstrate a significant reduction in wound infections, anastomotic leaks, and hospital stay length.

2. Critical Care, Trauma, and Burns

In severe trauma and burn patients, metabolic rates double, and glutamine reserves are depleted within hours. Enteral or parenteral glutamine supplementation in burn units has shown a clear reduction in infectious complications and mortality. However, in multi-organ failure or unstable septic shock, standard multi-ingredient immunonutrition is generally avoided until hemodynamic stability is achieved.

3. Emerging Frontiers: Viral Pathophysiology and Hyper-inflammation

Recent insights into severe viral infections (such as zoonotic henipaviruses or severe respiratory viruses) highlight the role of immunonutrition in mitigating viral-induced cytokine storms. When viruses trigger massive endothelial

inflammation and acute respiratory distress syndrome (ARDS), high-dose enteral omega-3 fatty acids and specific polyphenols (e.g., curcumin) help preserve alveolar-capillary barrier function, improve oxygenation indices, and prevent systemic multi-organ dysfunction.

Summary of Immunonutrients

Table 1: Major Immunonutrients, Their Biological Targets, Mechanisms of Action, and Clinical Applications

Immunonutrient	Target Tissues/Cells	Primary Biochemical Effect	Primary Clinical Indication
Glutamine	Enterocytes, lymphocytes, macrophages	Glutathione (GSH) synthesis; maintenance of intestinal tight junction integrity; primary cellular energy substrate	Severe burns, trauma, major gastrointestinal surgery, critically ill patients
Arginine	T-lymphocytes, endothelial cells	Nitric oxide (NO) production; upregulation of the **CD3ζ** chain on T-cells; enhancement of immune function and wound healing	Elective surgical oncology (pre- and postoperative), trauma, wound healing
Omega-3 Fatty Acids (EPA & DHA)	Cell membrane phospholipids, alveolar epithelial cells, immune cells	Inhibition of nuclear factor-kappa B (NF-κB); production of 3-series prostaglandins, 5-series leukotrienes, and specialized pro-resolving mediators (SPMs)	Acute respiratory distress syndrome (ARDS), severe acute viral hyperinflammation, systemic inflammatory conditions
Nucleotides	Rapidly dividing immune cells, enterocytes	Support of RNA and DNA synthesis; promotion of lymphocyte proliferation, T-cell maturation, and intestinal mucosal repair	Elective surgical patients, pediatric undernutrition, immune deficiency, gastrointestinal recovery

Challenges, Limitations, and Future Perspectives

Although immunonutrition has demonstrated promising biological mechanisms and therapeutic potential in enhancing immune function and improving clinical outcomes, the results of clinical trials have been inconsistent. One major limitation is the heterogeneity of patient populations, as studies often include diverse groups such as septic, trauma, and elective surgical patients, making it difficult to identify condition-specific benefits. Another important challenge is determining the optimal timing, dosage, and duration of immunonutrient administration, since the effectiveness of supplementation may vary depending on whether it is provided preoperatively, during the early postoperative period, or in the presence of active sepsis or shock. Furthermore, most commercially available immunonutrition formulas contain combinations of multiple bioactive nutrients, including arginine, glutamine, omega-3 fatty acids, and nucleotides, making it difficult to distinguish the individual contribution of each component to clinical outcomes. Future research should emphasize the development of personalized immunonutrition strategies by integrating patients' inflammatory biomarkers, immune status, gut microbiota composition, genetic factors, and metabolic profiles to optimize nutrient selection and dosing. Advances in precision medicine, systems biology, and artificial intelligence may further facilitate individualized nutritional interventions, leading to improved patient outcomes and more effective management of critically ill and surgical patients.

Conclusion

Immunonutrition moves beyond traditional caloric replenishment to actively manipulate the immune response using biological food components. When applied with precise timing and targeted patient selection—such as in elective major surgeries or early-stage hyper-inflammatory conditions—IN significantly improves clinical outcomes. As personalized medical nutrition therapies continue to advance, standardizing biomarkers to safely navigate the fine line between immune support and inflammatory overstimulation remains a priority.

References

1. Calder PC. Immunonutrition in surgical and critically ill patients. British Journal of Nutrition,2007:98(S1):S133–S139. https://doi.org/10.1017/s0007114507832909
2. Dushianthan A, Cusack R, Burgess VA, Grocott MPW, Calder PC. Immunonutrition for acute respiratory distress syndrome (ARDS) in adults. Cochrane Database of Systematic Reviews, 2019, (1). https://doi.org/10.1002/14651858.cd012041.pub2
3. Ham HJ, Kim J. Targeted nutritional strategies in postoperative care. Anesthesia and Pain Medicine,2025:20(1):34–45. https://doi.org/10.17085/apm.24067
4. Méndez López LF, González Llerena JL, Vázquez Rodríguez JA, Medellín Guerrero AB, González Martínez BE, Solís Pérez E, *et al*. Dietary modulation of the immune system. Nutrients,2024:16(24):4363. https://doi.org/10.3390/nu16244363
5. Perez Arteaga L. Perioperative immunonutrition for elective surgery: Review of mechanisms, summary of evidence, and future directions. Nutrients,2026:18(10):1603.
6. Tan BH, Danilla S, Murray A, Serra R, El Dib R, Henderson TOW, *et al*. Immunonutrition as an adjuvant therapy for burns. Cochrane Database of Systematic Reviews, 2014, (12). https://doi.org/10.1002/14651858.cd007174.pub2
7. Venter C, Eyerich S, Sarin T, Klatt KC. Nutrition and the immune system: A complicated tango. Nutrients,2020:12(3):818. https://doi.org/10.3390/nu12030818
8. Barbul A. Arginine and immune function. Nutrition,2008:24(3):215–218.
9. Calder PC. Omega-3 fatty acids and inflammatory processes: From molecules to man. Biochemical Society Transactions,2017:45(5):1105–1115. https://doi.org/10.1042/BST20160211
10. Schneider H, Atkinson SW. Immunonutrition—fact or fad. Archives of Virology,2000:157(9):1635–1641. https://doi.org/10.1007/BF02722634
11. Sengupta A. Impact of Immunonutrition (Arginine, Glutamine, Omega-3 Fatty Acids) in Critical Illness management. International Journal of Multidisciplinary Research and Development,2025:12(11):26–28.
12. Wernerman J. Clinical use of glutamine supplementation in critical illness. Current Opinion in Clinical Nutrition & Metabolic Care,2014:17(1):80–85. https://doi.org/10.1097/MCO.0000000000000014
13. García-Navas R, Munder M, Mollinedo F. Depletion of L-arginine induces autophagy as a cytoprotective

response to endoplasmic reticulum stress in human T lymphocytes. Autophagy,2012:8(11):1557–1576. https://doi.org/10.4161/auto.21315
14. Nicholls SJ, Tang WHW, Brennan ML, Brennan DM, Shishehbor MH, Xu M, *et al*. Metabolic profiling of arginine and nitric oxide pathways predicts hemodynamic abnormalities and mortality in patients with cardiogenic shock after acute myocardial infarction. Circulation,2007:116(20):2315–2324. https://doi.org/10.1161/CIRCULATIONAHA.107.693986
15. Poeze M, Bruins MJ, Kessels F, Luiking YC, Lamers WH, Deutz NE. Effects of L-arginine pretreatment on nitric oxide metabolism and hepatosplanchnic perfusion during porcine endotoxemia. The American Journal of Clinical Nutrition,2011:93(6):1237–1247. https://doi.org/10.3945/ajcn.110.007237
16. Rodriguez PC, Quiceno DG, Ochoa AC. L-arginine availability regulates T-lymphocyte cell-cycle progression. Blood,2006:109(4):1568–1573. https://doi.org/10.1182/blood-2006-06-031856
17. Suchner U, Heyland DK, Peter K. Immune-modulatory actions of arginine in the critically ill. British Journal of Nutrition,2002:87(S1):S121–S132. https://doi.org/10.1079/bjn2001465
18. Víteček J, Lojek A, Valacchi G, Kubala L. Arginine-based inhibitors of nitric oxide synthase: Therapeutic potential and challenges. Mediators of Inflammation,2012:2012:1–22. https://doi.org/10.1155/2012/318087