

## **Amino Acid-Based Therapies for Chronic Wounds: Navigating Delivery Challenges and Technological Innovations**

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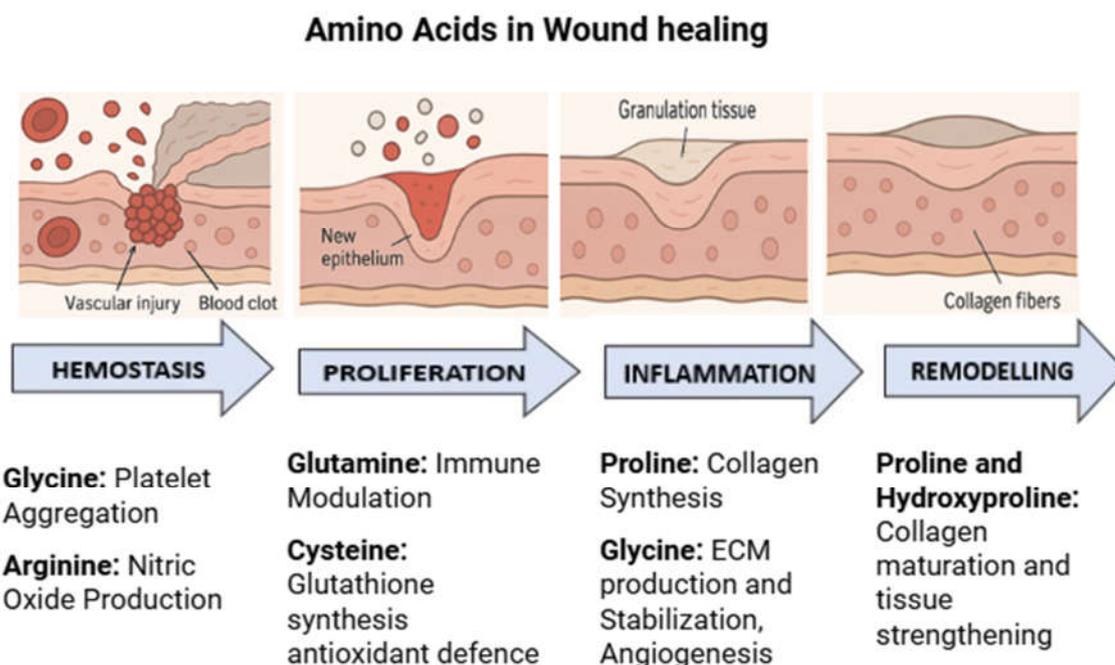
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## Graphical Abstract



**Amino acids support all phases of wound healing.**

## Abstract

Wound healing is a multifaceted biological process that requires a coordinated effort of several physiological systems, including nutritional support. Among the key nutrients influencing tissue repair, amino acids play a crucial role by serving as building blocks for proteins, promoting collagen synthesis, regulating oxidative stress, and modulating inflammation. This review explores the pharmaceutical technology approaches to amino acid delivery, focusing on the differences between oral and topical administration, particularly in the context of diabetic foot ulcers (DFUs). Despite the growing recognition of amino acids' potential in chronic wound management, especially DFUs, significant gaps remain in effective delivery methods. Oral formulations, while widely used, suffer from limited local bioavailability due to first-pass metabolism, whereas topical delivery systems face challenges such as poor deep tissue penetration and amino acid instability. The review discusses the current technological innovations, including nanoparticle-based systems, hydrocolloid dressings, and responsive wound dressings, aimed at overcoming these challenges. Moreover, the article emphasizes the need for more clinical evidence comparing oral and topical amino acid applications in DFUs, as well as the integration of amino acids with other therapies, such as growth factors. The future of wound healing could be revolutionized by personalized

medicine, advanced encapsulation techniques, and smart wound dressings, potentially offering targeted and sustained release of amino acids at the site of injury.

**Key words:** Amino Acids, Wound Healing, Diabetic Foot Ulcers, Pharmaceutical Delivery, Topical Therapy.

**Highlights :**

- \* The critical role of amino acids (arginine, glutamine, proline, glycine, cysteine, histidine) in collagen synthesis, immune modulation, oxidative stress regulation, and tissue repair.
- \* Detailed discussion on the differences and challenges between oral and topical amino acid delivery methods in wound management, especially for diabetic foot ulcers.
- \* Emphasis on pharmaceutical technology innovations like hydrocolloid dressings, encapsulation techniques, and personalized medicine approaches to enhance amino acid bioavailability and efficacy in chronic wound healing.
- \* Coverage of acute versus chronic wounds, with a strong focus on diabetic foot ulcers as a severe complication needing targeted amino acid therapy and an advanced delivery system

## **1. Introduction**

### **1.1 Background on Wound Healing and Nutritional Support**

Wound healing is a complex biological process that progresses through four overlapping and highly regulated phases: hemostasis, inflammation, proliferation, and remodeling. These phases are orchestrated by intricate interactions among various cell types, cytokines, growth factors, and extracellular matrix (ECM) components, ensuring effective tissue repair (Schultz et al., 2011). Nutritional support is critical during this process, as it plays a role in modulating key activities such as cellular proliferation, immune function, angiogenesis, collagen deposition, and ECM remodeling. Nutrient deficiencies, particularly of amino acids, vitamins, and trace elements, are strongly associated with impaired wound healing (Guo et al., and Dipietro et al., 2010). Deficiencies in specific nutrients can result in delayed epithelialization, poor tissue quality, and increased infection rates. A well-balanced nutritional intake is essential to support these phases of wound repair and prevent complications in chronic wounds (Saghaleini et al., 2018).

### **1.2 Importance of Amino Acids in Tissue Repair**

Amino acids play essential roles in tissue repair, beyond being structural units for protein synthesis. They act as bioactive molecules that regulate key molecular pathways in wound healing. Arginine enhances collagen synthesis, supports immune function, and promotes nitric oxide-driven vasodilation (Witte et al., 2002; Weijs et al., 2014). Glutamine fuels rapidly dividing cells, modulates immune responses, and aids antioxidant defense via glutathione. Proline and glycine contribute to collagen stabilization, fibrillogenesis, and wound tensile strength (Cruzat et al., 2018; De Bandt., 2006). These functions are vital for restoring the structural integrity of healing tissues. Clinical studies show amino acid supplementation improves outcomes, especially in malnourished or chronic wound patients. Arginine boosts hydroxyproline levels and collagen deposition, improving wound strength (Seifter et al., 1978). Glutamine reduces oxidative stress, preventing delays in the healing process. Thus, maintaining optimal amino acid levels can accelerate healing, particularly in vulnerable patient populations (Arribas-Lopez et al., 1978).

### **1.3 Objective and Scope of Review**

This review focuses on the pharmaceutical strategies for amino acid delivery in wound healing, particularly in diabetic foot ulcers (DFUs), a common and severe complication in diabetic patients (Hung et al., 2019). Amino acids like arginine, glutamine, lysine, proline, and  $\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB) have demonstrated therapeutic potential by supporting collagen synthesis, modulating immune responses, and enhancing angiogenesis (Williams et al., 2002). Oral supplementation and topical formulations, such as Vulnamin® gel (containing hyaluronic acid and amino acids), have been effective in promoting wound closure and tissue regeneration. However, challenges remain in optimizing delivery methods due to factors like gastrointestinal absorption and enzymatic degradation in chronic wounds. This review evaluates current strategies, identifies

challenges, and discusses emerging innovations to improve DFU management (Romanelli et al., 2024).

## **2. Types of Wounds and the Role of Amino Acids**

Wound healing is a complex biological process influenced by factors like wound type and patient health. Amino acids, especially arginine and glutamine, play crucial roles in tissue regeneration. Arginine enhances blood flow and immune responses by serving as a precursor for nitric oxide (Oyovwi et al., 2024). Supplementation with arginine has been shown to improve collagen deposition and wound tensile strength. Glutamine, the most abundant amino acid in plasma, is a primary energy source for fibroblasts and immune cells, promoting better nitrogen balance and reducing inflammation (Shi et al., 2000; Raizel et al., 2018). Emerging therapies explore combining amino acids with compounds like hyaluronic acid to accelerate healing in chronic wounds. Targeted supplementation offers a promising strategy for enhanced wound healing (Ozker et al., 2024; Seth et al., 2024).

### **2.1 Acute vs Chronic Wounds**

#### **2.1.1. Acute wounds**

Acute wounds, including surgical incisions and minor injuries, follow a predictable healing process through four phases: hemostasis, inflammation, proliferation, and remodeling. These phases ensure efficient tissue repair and skin restoration (Fitridge et al., 2011). The hemostatic phase involves vascular constriction and platelet aggregation, forming a clot that halts bleeding. Inflammation follows with neutrophils and macrophages clearing debris and preventing infection. The proliferative phase includes fibroblast activity, extracellular matrix synthesis, and angiogenesis, restoring blood flow (Rodrigues et al., 2018; Cialdi et al., 2022). In remodeling, collagen maturation and reorganization enhance tensile strength. Although this process is typically efficient, conditions like diabetes can disrupt healing, leading to prolonged recovery. Understanding these phases allows clinicians to identify complications and optimize patient outcomes (Mathew-Steiner et al., 2021; Spampinato et al., 2020).

#### **2.1.2. Chronic wounds**

Chronic wounds, including pressure ulcers, venous leg ulcers, and diabetic foot ulcers, are characterized by disruptions in the normal healing process. These wounds often fail to progress through the typical phases, resulting in prolonged non-healing. Fibroblasts in chronic wounds show premature senescence, with elevated levels of plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor- $\beta$  (TGF- $\beta$ ), which hinder matrix remodeling (Werdin et al., 2009; Pastar et al., 2023). Hypoxia within the wound environment also delays collagen maturation and angiogenesis. The inflammatory phase in chronic wounds is often prolonged, marked by elevated matrix metalloproteinases (MMPs) and reduced tissue inhibitors of metalloproteinases (TIMPs) (Frykberg et al., 2015; Han et al., 2023). Chronic wounds often harbor biofilms that protect bacteria

from the immune system, complicating infection management. Targeting these molecular and cellular mechanisms is essential for developing effective treatments (Krishnaswamy et al., 2017; Diban et al., 2023).

## **2.2 Pressure Ulcers**

Pressure ulcers, also known as pressure injuries or bedsores, result from prolonged mechanical pressure that impedes blood flow to localized areas of tissue. This ischemia initiates a cascade of cellular and molecular events leading to tissue necrosis and inflammatory damage (Chow et al., 2012). The pathophysiology encompasses endothelial cell dysfunction, increased vascular permeability, and the release of pro-inflammatory cytokines, which collectively compromise tissue integrity and delay healing. In the context of wound healing, specific amino acids play pivotal roles in modulating these pathological processes (Zaidi et al., 2025; Bao et al., 2008).

Arginine, a conditionally essential amino acid, serves as a precursor for nitric oxide (NO) synthesis, a molecule crucial for vasodilation and collagen formation (Langkamp-Henken et al., 2000). Supplementation with arginine has been shown to enhance collagen deposition and accelerate wound healing by stimulating fibroblast activity and immune responses (Witte et al., 2003). Glutamine, the most abundant amino acid in human plasma, supports immune cell proliferation and intestinal barrier function. It has been demonstrated to reduce levels of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ , thereby mitigating systemic inflammation and promoting tissue repair (Tao et al., 2014). Proline and its hydroxylated form, hydroxyproline, are integral to collagen synthesis and stabilization. These amino acids contribute to the formation of the extracellular matrix, providing structural support essential for tissue regeneration (Albaugh et al., 2017). Cysteine, an amino acid with antioxidant properties, plays a critical role in protecting cells from oxidative stress. By facilitating the synthesis of glutathione, cysteine helps neutralize reactive oxygen species, thereby preserving cellular integrity during the inflammatory phase of wound healing (Tieu et al., 2023).

Collectively, these amino acids not only support the structural and functional aspects of tissue repair but also modulate the inflammatory response, underscoring their importance in the management and treatment of pressure ulcers.

## **2.3 Venous and Arterial Ulcers**

Chronic venous hypertension and arterial insufficiency are key factors in the development of lower extremity ulcers through mechanisms like endothelial dysfunction, inflammation, and impaired tissue regeneration (Crawford et al., 2017). Elevated venous pressure leads to capillary leakage, leukocyte activation, and the release of pro-inflammatory cytokines, resulting in tissue edema, hypoxia, and ulceration. Arterial insufficiency causes ischemia and delayed wound healing (Scallan et al., 2010; Eberhardt et al., 2014).

Amino acids such as arginine, glycine, cysteine, and histidine play crucial roles in wound healing. Arginine boosts endothelial function and enhances nitric oxide production, which aids in vasodilation and angiogenesis (Chu et al., 2021). Glycine reduces pro-inflammatory cytokines like TNF- $\alpha$ , promoting inflammation resolution and tissue repair (Melo et al., 2022). Cysteine, by increasing glutathione synthesis, mitigates oxidative damage, supporting healing in ischemic tissues. Histidine, through its role in histamine production and carnosine synthesis, has antioxidative and tissue-regenerative effects, offering potential benefits for wound recovery (Quintanilla-Villanueva et al., 2024).

These amino acids represent promising therapeutic targets for enhancing wound repair in patients with chronic venous or arterial ulcers.

## **2.4 Surgical Wounds**

In surgical wound healing timely advancement through these stages is critical to minimize the risk of infection, excessive scarring, and impaired tissue regeneration. Key amino acids, such as glutamine, proline, glycine, and cysteine, play essential roles in optimizing healing outcomes (Antoury et al., 2025).

Glutamine, conditionally essential during stress, supports immune function, enhances lymphocyte proliferation, and strengthens the gut barrier (Manhart et al., 2021). Proline and hydroxyproline are crucial for collagen biosynthesis, accelerating tissue remodeling and improving wound tensile strength (Linju et al., 2023). Glycine reduces inflammation, preserves tissue integrity, and facilitates healing progression (Aguayo-Ceron et al., 2023). Cysteine contributes to antioxidant defenses by supporting glutathione synthesis, neutralizing oxidative stress, and sustaining tissue repair (Mao et al., 2016).

These amino acids are integral to immune regulation, oxidative balance, and structural regeneration in surgical wound healing.

## **2.5 Diabetic Foot Ulcers (DFUs)**

Chronic hyperglycemia, a defining feature of diabetes mellitus, disrupts key physiological processes involved in wound healing. High glucose levels impair leukocyte activity, reducing chemotaxis, phagocytosis, and cytokine production, which weakens innate immunity (Falanga et al., 2005). Angiogenesis is also compromised due to suppressed VEGF expression and endothelial dysfunction, delaying tissue regeneration. Fibroblast activity and collagen synthesis decline, resulting in poor extracellular matrix (ECM) formation. These effects collectively lead to persistent, non-healing ulcers in diabetic patients.

Several amino acids help counteract these impairments and support wound healing. Arginine enhances nitric oxide production, improving vasodilation and collagen formation. Glutamine aids immune function and redox balance, essential for cell growth and ECM synthesis (Berm er al., 2007). Glycine reduces inflammation and strengthens the ECM through its role in collagen

structure. Cysteine acts as an antioxidant, protecting repair cells from oxidative stress. Proline contributes to collagen stability and overall tissue strength during healing (Perez-Torres et al., 2017; cheong et al., 2014). Histidine helps resolve chronic inflammation through immune modulation. These amino acids, when used therapeutically, offer targeted support for diabetic wound healing. Their combined roles present a promising approach to managing wounds in hyperglycemic conditions. Further clinical research can solidify their use in personalized wound care strategies (Saadati et al.,2024).

Different types of wounds benefit from specific amino acid supplementation to support these healing phases. Table 1 summarizes the key amino acids and their primary functions associated with various wound types.

**Table 1.** Amino Acids and Their Roles in Different Wound Types

Wound Type	Key Amino Acids	Primary Functions
Pressure Ulcers	Arginine, Glutamine, Proline, Cysteine	Vasodilation (Arginine), Immune Support (Glutamine, Cysteine), Collagen Synthesis (Proline)
Venous/Arterial Ulcers	Arginine, Glycine, Cysteine, Histidine	Endothelial Repair (Arginine), Anti-Inflammation (Histidine, Glycine), Tissue Regeneration (Cysteine)
Surgical Wounds	Glutamine, Proline, Glycine, Cysteine	Infection Control (Glutamine), Collagen Deposition (Proline, Glycine), Tissue Repair (Cysteine)
Diabetic Foot Ulcers (DFUs)	Arginine, Glutamine, Glycine, Cysteine, Proline, Histidine	Vasodilation (Arginine), Antioxidant Defense (Cysteine), Extracellular Matrix Remodeling (Proline), Immune Modulation (Histidine)

### 3. Biological Roles of Amino Acids in Wound Healing

#### 3.1. Key Phases of Wound Healing

##### 3.1.1. Hemostasis

Hemostasis is the immediate response to injury, where clotting occurs to prevent blood loss. Amino acids such as glycine and arginine play key roles in stabilizing platelet function and promoting clot formation. Glycine modulates platelet aggregation, and arginine enhances nitric oxide production, which supports vasodilation and platelet function (LaPelusa et al., 2019).

### **3.1.2. Inflammation**

The inflammatory phase involves immune system activation to prevent infection and clear debris. Amino acids like glutamine and cysteine aid in regulating the immune response. Glutamine supports immune cell function and helps reduce oxidative stress, while cysteine contributes to glutathione synthesis, an important antioxidant in the inflammatory process (Cruzat et al., 2014).

### **3.1.3. Proliferation**

During the proliferation phase, new tissue forms through fibroblast proliferation, angiogenesis, and ECM production. Proline, glycine, and arginine are critical in this phase. Proline supports collagen synthesis, glycine stabilizes the ECM, and arginine enhances fibroblast activity and blood vessel formation, improving nutrient and oxygen delivery to the wound site (Kay et al., 2021).

### **3.1.3. Remodeling**

The remodeling phase involves collagen maturation and tissue strengthening. Proline and hydroxyproline, which are involved in collagen crosslinking, help mature the collagen fibers, leading to tissue strengthening. This phase ensures the transition from a weak provisional matrix to a stable, functional tissue (Sun et al., 2024).

## ***3.2. Specific Amino Acids and Their Functions***

### **3.2.1. Arginine**

Arginine is a precursor to nitric oxide, which enhances blood flow and promotes fibroblast activity. Nitric oxide also plays a role in vasodilation, improving tissue perfusion and nutrient delivery. Arginine contributes to regulating inflammation and immune responses during wound healing (Wu et al., 2021).

### **3.2.2. Glutamine**

Glutamine is essential for immune function and is a critical energy source for rapidly dividing cells, such as immune cells and enterocytes. It helps maintain redox balance by serving as a precursor for glutathione, which protects cells from oxidative damage. Glutamine also supports collagen and protein synthesis during the healing process (de Oliveira et al., 2016).

### **3.2.3. Glycine**

Glycine stabilizes the ECM and has anti-inflammatory effects. It helps reduce the levels of pro-inflammatory cytokines and contributes to collagen formation. Glycine plays a key role in ensuring that the ECM remains structurally intact as tissue healing progresses (Fajar et al., 2022).

### **3.2.4. Proline/Hydroxyproline**

Proline is a core component of collagen and is vital for collagen synthesis and stability. Hydroxyproline, derived from proline, plays an essential role in collagen crosslinking, enhancing

the strength and integrity of the newly formed tissue. These amino acids are crucial for the structural integrity of the healed tissue (Furtado et al.,2022).

### **3.2.5. Cysteine**

Cysteine is involved in the synthesis of glutathione, an important antioxidant that helps regulate oxidative stress during wound healing. By maintaining redox balance, cysteine supports cellular function, particularly in immune cells and fibroblasts at the wound site (Fujii et al., 2023).

### **3.2.6. Histidine**

Histidine helps buffer the acidic environment often present during wound healing, supporting tissue repair. It also plays a role in the synthesis of histamine, which mediates blood vessel dilation and immune cell recruitment to the wound site (Kessler et al., 2019).

## **3.3. Amino Acid Deficiencies and Impaired Healing**

Amino acid deficiency disrupts all phases of tissue repair, compromising wound healing. In the hemostasis phase, low arginine impairs nitric oxide synthesis, affecting vascular tone and clot stability (Luiking et al., 2012). During inflammation, glutamine and cysteine shortages reduce immune cell function and increase oxidative stress. Proliferative phase deficiencies in proline, glycine, and arginine hinder fibroblast migration and ECM formation. Poor proline and hydroxyproline availability weakens collagen maturation in the remodeling phase (Amirrah et al., 2022). Redox imbalance from amino acid deficits worsens oxidative injury at the wound site. In diabetic foot ulcers, hyperglycemia exacerbates amino acid loss, impairing healing further. This leads to chronic inflammation, poor neovascularization, and increased infection risk. Targeted supplementation with arginine, glutamine, and leucine improves healing outcomes. Adequate amino acid levels are vital for collagen synthesis, immune defense, and redox control (Deng et al., 2021).

## **4. Amino Acid Composition of Silk Fibroin and Its Relevance in Diabetic Wound Healing**

Silk fibroin, derived from *Bombyx mori*, is a natural protein biomaterial extensively explored for wound healing applications due to its unique amino acid composition and structural properties. It is primarily composed of glycine (~46%), alanine (~30%), and serine (~12%), with smaller amounts of tyrosine (~5%) and other amino acids (Vidya et al., 2021). The high content of glycine and alanine facilitates the formation of  $\beta$ -sheet structures, which confer excellent mechanical strength and stability to silk fibroin. Serine and tyrosine contribute to hydrogen bonding, antioxidant activity, and provide functional groups for biochemical modifications. These properties are particularly beneficial in diabetic wound healing, where oxidative stress, delayed angiogenesis, and impaired tissue regeneration are major challenges (Aldahish et al., 2024). Several studies have demonstrated that silk fibroin-based scaffolds and nanofibers promote cell adhesion, proliferation, and migration, thereby mimicking the extracellular matrix. Moreover, silk

fibroin dressings functionalized with bioactive agents such as Aloe vera or insulin have shown enhanced healing in diabetic wound models by promoting granulation tissue formation and collagen deposition (Tairq et al., 2021; Li X et al., 2017). These findings support the application of silk fibroin as a bioactive and biocompatible material for accelerating tissue repair in diabetic wounds.

### **Formulations of Silk Fibroin in Diabetic Wound Healing**

Silk fibroin (SF), a natural protein derived from *Bombyx mori*, has been extensively explored in various formulations for diabetic wound management due to its biocompatibility, biodegradability, and mechanical strength. The versatility of SF allows it to be processed into multiple forms, each tailored to specific wound healing requirements:

- **Nanofibers (Electrospun Mats):** Electrospinning technology enables the fabrication of SF nanofibers that closely mimic the extracellular matrix, providing a conducive environment for cell adhesion, proliferation, and migration. These nanofibrous mats can be loaded with therapeutic agents, offering controlled drug release and enhanced healing in diabetic wounds (Chen et al., 2020).
- **Hydrogels:** SF-based hydrogels offer a moist environment essential for wound healing. Incorporating antibacterial and antioxidant agents into SF hydrogels has demonstrated accelerated healing in diabetic wounds by reducing inflammation and promoting tissue regeneration (Guo et al., 2023).
- **Sponges or Scaffolds:** Porous SF sponges serve as three-dimensional scaffolds that support cell infiltration and angiogenesis. When combined with bioactive molecules like insulin, these sponges have shown improved wound closure and collagen deposition in diabetic models (Liu et al., 2019).
- **Films or Membranes:** SF films provide a protective barrier while allowing gas exchange. Functionalization with growth factors, such as insulin-like growth factor-1 (IGF-1), has been shown to enhance re-epithelialization and vascularization in diabetic wounds (Lin MJ et al., 2021).
- **Microparticles or Nanoparticles:** SF can be processed into microparticles or nanoparticles for controlled and sustained release of therapeutic agents. For instance, SF-based dressings incorporating neurotensin-loaded gelatin microspheres have demonstrated improved wound healing in diabetic rat models (Oy et al., 2025).

## **5. Topical Delivery Systems**

### **5.1. Cosmetic Use of Topical Amino Acids in Wound Healing**

The topical application of amino acids in cosmetic formulations has emerged as a promising strategy for enhancing wound healing, particularly in chronic and hard-to-heal wounds. Amino acids, the fundamental units of proteins, are integral to various physiological processes, including tissue repair and regeneration (Tabriz et al., 2022). Their topical application provides essential nutrients that support the formation of new tissue, leading to improved wound closure and reduced scar formation. For instance, glycinamide, a derivative of glycine, has been shown to significantly enhance collagen production in human dermal fibroblasts, thereby promoting wound healing without inducing unwanted cell differentiation (He et al., 2024). Moreover, the combination of amino acids with hyaluronic acid (HA) in topical dressings has demonstrated synergistic effects, accelerating re-epithelialization and stimulating fibroblast proliferation, which are crucial for effective wound healing (Chylinska et al., 2025).

## 5.2. Rationale for Using Cosmetic Formulations in Wound Care

The rationale behind using cosmetic formulations for wound healing lies in their ability to deliver active compounds directly to the affected area, ensuring localized treatment with minimal systemic side effects (Dovedytis et al., 2020). Such formulations can be tailored to maintain a moist wound environment, protect against infection, and provide sustained release of therapeutic agents. Clinical studies have reported significant reductions in wound size and enhanced healing rates with the use of amino acid-enriched dressings (Saghazadeh et al., 2018). The advantages and limitations of using topical amino acids in wound care are summarized in Table 2.

**Table 2.** Advantages and Limitations of Topical Amino Acid Therapies in Wound Healing

Advantages	Limitations and Challenges	Refereces
Localized and controlled delivery of bioactive compounds	Efficacy may vary with wound type, severity, and patient-specific factors	Martinez-Ballesta et al.,2018
Promotion of collagen synthesis and fibroblast activity	Patient compliance can impact treatment outcomes	Mir et al., 2018
Reduction in inflammation and oxidative stress	Co-morbid conditions (e.g., diabetes) may reduce effectiveness	Bhatti et al., 2022
Improved cosmetic outcomes with better tissue remodeling and minimal scarring	Lack of standardized concentrations and optimized delivery systems in some formulations	Shariatzadeh et al., 2024

## 6. Gaps and Challenges in Current Pharmaceutical Technology

### **6.1. Low Penetration of Topical Amino Acids into Deep Wounds**

The hydrophilic nature of amino acids limits their penetration through the stratum corneum in topical wound healing. Formulations like liposomes, niosomes, hydrogels, and microemulsions enhance permeability and sustained delivery (Shukla et al., 2018). These systems improve dermal absorption by disrupting lipid layers or acting as drug reservoirs. Ionic liquids and amphiphilic derivatives further aid amino acid delivery, promoting collagen synthesis and tissue repair. Despite progress, challenges in stability and targeted delivery remain, warranting continued research (Hmingthansanga et al., 2022).

### **6.2 Amino Acid Instability in Topical Formulations**

Amino acids in topical formulations are prone to degradation via oxidation and hydrolysis, reducing stability and efficacy. Oxidation targets residues like methionine and cysteine, triggered by light, ROS, and metal ions (Nugrahadi et al., 2023). Hydrolysis, influenced by pH and temperature, breaks down amino acid chains and weakens the formulation. Stabilizing strategies include using antioxidants, metal chelators, protective packaging, and lyophilization. Ensuring amino acid stability is essential for developing effective topical therapeutics (Zapadka 2017).

### **6.3 Scarcity of Controlled-Release Formulations**

Controlled-release formulations for amino acid delivery are critically lacking in chronic wound therapy, where sustained nutrient supply is essential for healing. Innovations in hydrogels and nanocarriers are aiming to address this issue by enabling prolonged amino acid release (Ribeiro et al., 2024). These systems encapsulate amino acids in biocompatible matrices, ensuring sustained delivery at the wound site. Clinical data suggest such approaches accelerate healing and improve outcomes, but their commercial availability remains limited. Bridging this gap could significantly improve chronic wound care and patient recovery (Harun-Ur-Rashid et al., 2025).

### **6.4 Limited Clinical Data for Topical Amino Acid Therapies**

Topical amino acid therapies are gaining interest for enhancing skin health and wound healing. Studies show benefits when combined with agents like hyaluronic acid, improving wound closure and tissue regeneration (Shang et al., 2024). A study on 160 patients reported significant wound area reduction using amino acid dressings over six weeks. Acetyl aspartic acid has also shown potential in cosmetic dermatology by boosting extracellular matrix protein deposition. However, more large-scale randomized trials are needed to confirm their efficacy and safety in clinical settings (Antoszezwska et al., 2024).

### **6.5 Regulatory and Commercialization Hurdles**

The regulatory and commercialization hurdles for hybrid drug-device combination products, such as advanced topical systems, are significant due to their complex nature. These products blur the lines between drugs and medical devices, complicating classification (Reis et al., 2022). Ambiguity in the primary mode of action (PMOA) can delay approval processes. The lack of

international regulatory harmonization leads to overlapping requirements, further increasing costs and delays. Overcoming these challenges requires clearer guidelines, international collaboration, and a more integrated approach to streamline development and approval (Tain et al., 2022).

## **7. Focused Discussion: Diabetic Foot Ulcers and Amino Acid Therapy**

### **7.1. The Complex Healing Environment of DFUs**

Diabetic foot ulcers (DFUs) are a complex complication of diabetes mellitus, where hyperglycemia, peripheral neuropathy, ischemia, and infections create a challenging environment for wound healing. Hyperglycemia exacerbates oxidative stress, leading to endothelial dysfunction and impaired circulation, which delays healing (Colloud et al., 2023). Peripheral neuropathy reduces sensation and alters foot biomechanics, increasing ulcer risk. Additionally, peripheral arterial disease (PAD) limits blood flow, further impeding healing. Hyperglycemia also weakens immune function, impairing infection control. Chronic infections and biofilm formation prolong inflammation and hinder recovery. Addressing these interrelated factors is essential for effective DFU management and healing (Burgess et al., 2021).

### **7.2 The Potential of Topical vs Oral Amino Acid Applications in DFUs**

Diabetic foot ulcers (DFUs) pose significant challenges in wound healing due to poor circulation and neuropathy. Amino acids are vital for cellular function and tissue repair, playing a crucial role in enhancing wound healing [97]. Oral supplementation of amino acids like arginine and glutamine can improve systemic metabolic functions, supporting collagen synthesis and immune function. However, oral supplementation may have limited efficacy in DFUs, particularly in patients with poor circulation (Ellinger et al., 2014).

Topical amino acid applications, however, offer a localized approach, directly delivering healing agents to the ulcer site, potentially overcoming the limitations of systemic delivery. Studies show that topical amino acid-based dressings can significantly promote wound healing, reducing ulcer size and improving tissue regeneration (Cassino et al., 2010). Combining both oral and topical amino acids could offer synergistic benefits, providing a comprehensive treatment plan. Further research is needed to optimize these therapies in clinical settings.

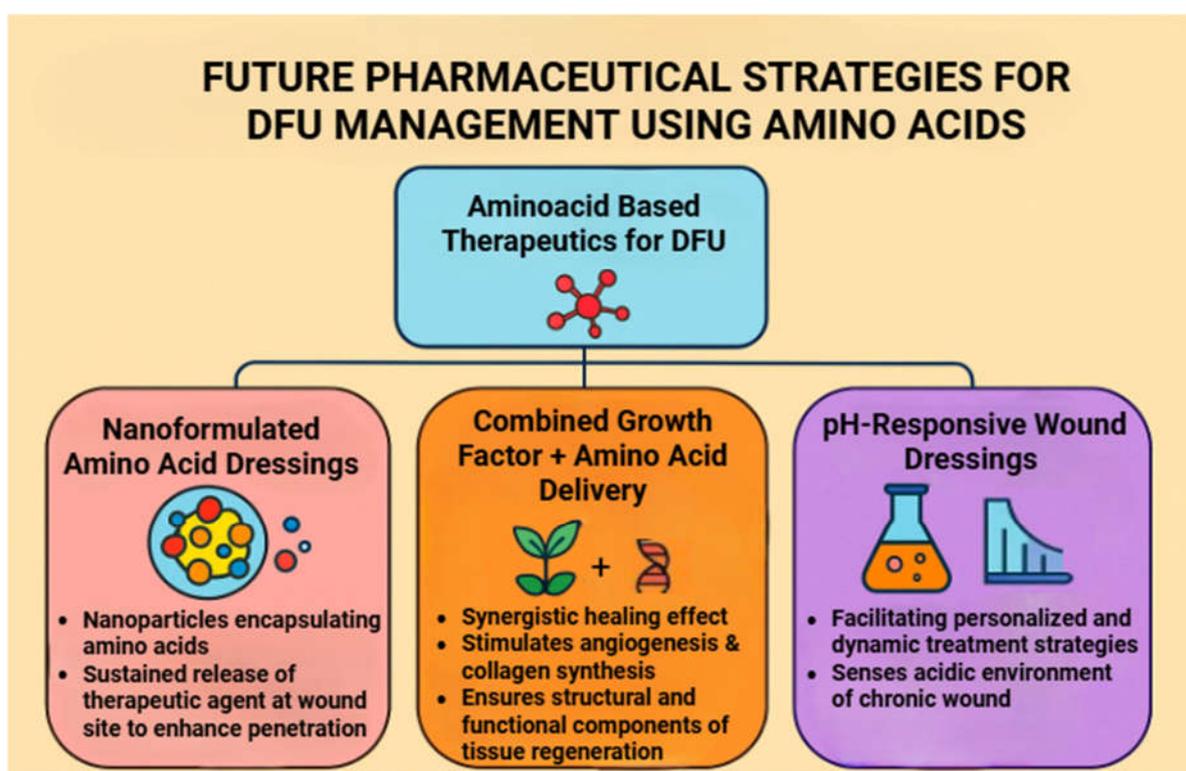
### **7.3. Clinical Evidence and Case Studies**

The potential for improving diabetic foot ulcer (DFU) healing through nutritional supplementation, particularly with amino acids like arginine and glutamine, has gained attention. Arginine plays a pivotal role in nitric oxide (NO) synthesis, promoting vasodilation, angiogenesis, and immune function key factors in wound healing. Glutamine supports cell proliferation and collagen formation, both critical for tissue repair. While several studies suggest that supplementation with arginine and glutamine can expedite wound healing, particularly in high-risk populations, the optimal delivery method (oral or topical) remains underexplored (Stechmiller et al., 2005). Research by Wang et al. (2017) indicates both methods are beneficial in animal models, but there is a clear gap in clinical evidence comparing these routes directly (Li et al., 2017). Future research

should focus on evaluating both the efficacy and mechanistic differences between oral and topical applications of these amino acids to enhance DFU healing outcomes.

#### 7.4. Future Pharmaceutical Strategies for DFU Management Using Amino Acids

Diabetic foot ulcers (DFUs) are a significant clinical challenge, often leading to prolonged healing times and an increased risk of infection, complications, and amputations (Baig et al., 2022). Recent advancements in pharmaceutical strategies are focused on enhancing DFU management through innovative wound dressing technologies. These technologies aim to accelerate wound healing, reduce the burden of chronic wounds, and improve patient outcomes (Kolimi et al., 2022). **Fig 1** illustrates emerging amino acid-based therapeutic strategies, including nanoformulated amino acid dressings, combined growth factor and amino acid delivery systems, and pH-responsive wound dressings specifically tailored for the diabetic wound environment.



**Fig 1.** Strategic Pharmaceutical Innovations of Amino Acids in Diabetic Wound Healing

##### 7.4.1. Nanoformulated Amino Acid Dressings

Nanotechnology has paved the way for the development of advanced wound care strategies. Nanoformulated amino acid dressings harness the potential of nanoparticles to deliver amino acids directly to the wound site, promoting faster cellular repair and regeneration (Hamdan et al., 2017). The small size of nanoparticles allows for better tissue penetration and sustained release of therapeutic agents, resulting in improved healing dynamics for diabetic foot ulcers. These

dressings also facilitate controlled delivery, ensuring that the active ingredients remain effective for extended periods, thus providing continuous therapeutic support (Ataide et al., 2022).

#### **7.4.2. Combined Growth Factor and Amino Acid Delivery**

The integration of growth factors with amino acids in wound dressings offers a novel approach to enhancing tissue repair. Growth factors are essential for stimulating cell proliferation, tissue regeneration, and angiogenesis, while amino acids play a vital role in protein synthesis and collagen formation (Veith et al., 2019). By combining these two elements in a single therapeutic platform, it is possible to address multiple aspects of wound healing simultaneously, providing a comprehensive solution that accelerates the repair of diabetic foot ulcers. This combined delivery system ensures that both the structural and functional components of tissue regeneration are adequately supported (Yamakawa et al., 2019).

#### **7.4.3. pH-Responsive Wound Dressings Tailored for Diabetic Wounds**

Diabetic wounds often present with an alkaline pH, which can impair the healing process. To address this, pH-responsive wound dressings have been developed, which adapt to the changing pH of the wound environment. These smart dressings release therapeutic agents in response to acidic conditions commonly found in diabetic wounds, providing localized and targeted treatment when needed. Such dressings not only enhance the efficacy of the treatment but also allow for real-time monitoring and adjustment of the wound environment, facilitating personalized and dynamic treatment strategies. These innovations offer promising solutions for managing DFUs and improving overall wound care (Li et al., 2024).

### **8. Future Directions and Technological Innovations**

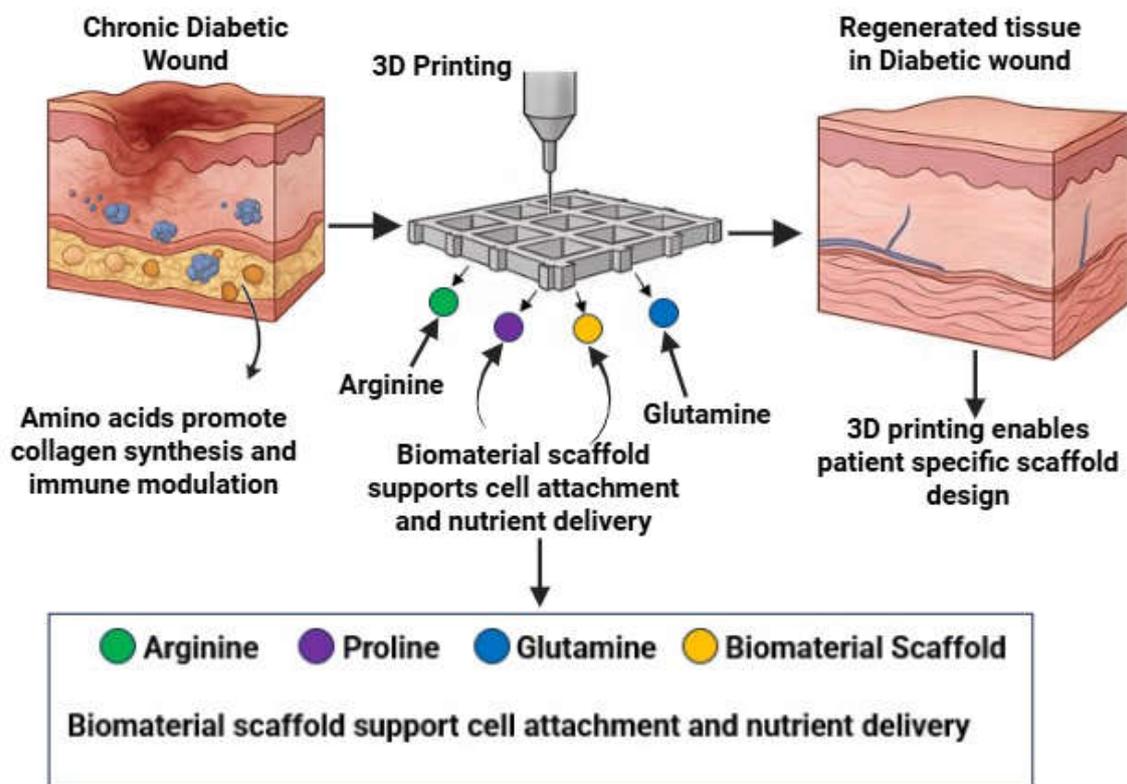
#### **8.1 Encapsulation Techniques for Improved Stability and Release**

Nano- and microencapsulation techniques are emerging as essential methods to enhance the stability and controlled release of amino acids. Nano- and microencapsulation are key technologies to improve the stability and controlled release of amino acids. Nanoencapsulation (<100 nm) ensures targeted delivery, higher stability, and better cellular uptake (Chowdhury et al., 2024). Nanocarriers like liposomes, SLNs, and polymeric nanoparticles offer sustained release and enhanced bioavailability (Bukke et al., 2024). Microencapsulation (1–1000 µm) is better suited for large-scale production and easier handling. The choice between nano and micro systems depends on release profile, administration route, and amino acid properties. Advances in materials and carrier design continue to refine. These encapsulation methods hold great promise for therapeutic and nutritional applications (Choudhury et al., 2021).

#### **8.2. Biomaterials and 3D Printed Scaffolds Loaded with Amino Acids**

3D printing technologies are transforming tissue engineering by creating personalized biomaterial-based scaffolds, particularly for chronic wound management. Amino acids, essential for collagen formation and cellular activities, can be integrated into these scaffolds, promoting wound healing

(Liu et al., 2022). For instance, arginine enhances blood flow by promoting nitric oxide production, while proline and glycine contribute to collagen synthesis. These amino acids can be incorporated into 3D scaffolds through bioinks or post-printing functionalization, releasing them at the wound site to stimulate tissue regeneration and improve healing efficiency (**Fig 2**). Personalized scaffolds have applications beyond wound care, including skin regeneration and bone tissue engineering (Chen et al., 2023).



**Fig 2.** Biomaterials and 3D Printed Scaffolds Loaded with Amino Acids in Diabetic Wound healing.

### 8.3. Combination Products (Amino Acids + Growth Factors/Antimicrobials)

Combination products containing amino acids, growth factors, and antimicrobials offer a comprehensive approach to wound healing, particularly for chronic wounds. Amino acids like arginine and glutamine support protein synthesis and immune function, while growth factors such as PDGF and VEGF stimulate cell proliferation and tissue regeneration (Nizam et al., 2025). Antimicrobials, including silver and chitosan, help prevent infections, enhancing the healing process. The synergistic effect of these components addresses both tissue regeneration and infection control, providing an effective solution for chronic wound management (Zhang et al., 2023). A summary of key components, their roles in wound healing, and mechanisms of action is presented in Table 3.

**Table 3.** Key Bioactive Components and Their Mechanisms in Wound Healing

<b>Component</b>	<b>Example(s)</b>	<b>Role in Wound Healing</b>	<b>Mechanism of Action</b>
<b>Amino Acids</b>	Arginine, Glutamine, Proline	Essential for protein synthesis, collagen formation, and immune response.	Stimulate collagen production, improve angiogenesis, enhance immune function (e.g., promoting macrophage activity).
<b>Growth Factors</b>	PDGF (Platelet-derived growth factor), VEGF (Vascular endothelial growth factor), FGF (Fibroblast growth factor)	Crucial for cell proliferation, tissue regeneration, and angiogenesis.	Enhance cell migration, proliferation, and matrix deposition; promote the formation of new blood vessels.
<b>Antimicrobials</b>	Silver, Gentamicin, Honey, Chitosan	Prevent or reduce infection in wounds, particularly in chronic wounds susceptible to microbial colonization.	Act through antimicrobial properties, reduce biofilm formation, and enhance healing by preventing infection-related complications.

#### **8.4. Personalized Medicine Approaches**

Personalized medicine offers a transformative approach for managing chronic wounds, especially in nutritionally deficient patients. Tailored amino acid therapy using arginine, glutamine, and HMB enhances wound healing through targeted mechanisms. Arginine boosts nitric oxide production for improved blood flow, while glutamine maintains immune function and gut integrity. HMB minimizes muscle protein breakdown, supporting tissue repair and regeneration. Clinical studies show that these amino acids improve collagen content and immune responses in patients with chronic wounds (Alexander et al., 2014). Evidence from diabetic foot ulcer patients and meta-analyses supports their role in promoting healing. This individualized strategy optimizes outcomes and minimizes the limitations of generalized treatments.

#### **8.5 Smart Responsive Delivery Systems for Chronic Wounds**

Recent advances in chronic wound care have led to smart delivery systems that respond dynamically to the wound environment. These systems use stimuli-responsive materials like pH- or thermosensitive hydrogels and shape-memory polymers for on-demand drug release. They activate based on local cues such as temperature, pH, or moisture, enabling precise therapeutic control (Zhang et al., 2023). A breakthrough innovation is the integration of flexible bioelectronics into wound dressings. These embedded sensors monitor wound conditions and trigger real-time drug release, forming a closed-loop system. The fusion of materials science, bioelectronics, and biomedical engineering is reshaping wound management. Such smart systems promise better healing outcomes and fewer complications in chronic wound care (Hossain et al., 2024).

#### **9. Conclusion**

Amino acids are integral to the wound healing process, with essential roles in collagen synthesis, immune modulation, and oxidative stress regulation. The choice between oral and topical delivery methods for amino acids presents significant challenges, particularly in chronic wounds like diabetic foot ulcers, where localized treatment is often more effective. While oral supplementation can address systemic deficiencies, topical systems provide the potential for direct wound-site therapy, bypassing systemic barriers. However, limitations such as deep tissue penetration, stability issues, and formulation difficulties must be addressed. Current technological advancements, including nanoparticle delivery systems and responsive dressings, hold promise in overcoming these obstacles. The future of wound healing lies in more personalized, targeted approaches that combine amino acid therapies with other treatment modalities, optimizing healing outcomes. Further clinical studies are crucial to validate these technologies and fully harness the therapeutic potential of amino acids in wound care.

## 10. CRediT authorship contribution statement

**Nivetha Shanmugam** – conceptualization, writing original draft; **Satheesh Babu Natarajan** – reviewed the manuscript.

## 11. Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## 13. References:

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