SCIENTIFIC Publishing Limited

Trends in Immunotherapy

https://ojs.ukscip.com/index.php/ti

Article

Immunotherapy for Chronic Wounds in Aging Populations: A Scoping Review of Mechanisms, Therapeutic Agents, and Clinical Gaps

Kwanchai Rattanamanee [1,2], Patsanan Kulla [3], Thanaporn Thakolpattanakul [2], Thanakrit Thakolpattanakul [2], Khemjira Pinyoying [2], and Prayuth Poowaruttanawiwit [1,2*]

[1] Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phisanulok 65000, Thailand

[2] Medical Research and Pharmaceutical Care Unit, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok 65000, Thailand

[3] Boromarajonani College of Nursing, Phisanulok 65000, Thailand

[*] Correspondence: yuth_pu@hotmail.com

Received: 12 June 2025; **Revised:** 27 June 2025; **Accepted:** 02 July 2025; **Published:** 09 October 2025

Abstract: Chronic wounds in older adults are a growing concern due to impaired immunity, delayed epithelialization, and prolonged inflammation. These wounds lead to significant morbidity, increased healthcare costs, and reduced quality of life. Immunotherapies and adjunctive interventions show promise but remain insufficiently validated in geriatric populations. This study aimed to synthesize and map current evidence on immune-based strategies and supportive approaches for chronic wound management in the elderly, focusing on mechanisms, outcomes, and delivery challenges. A scoping review was conducted following the Arksey and O'Malley framework and PRISMA-ScR guidelines. Searches in PubMed, Scopus, and Web of Science, complemented by manual screening, identified eligible studies using the PCC (Population–Concept–Context) framework. Data extracted included therapeutic class, mechanism, wound type, and outcomes. Of 1,142 records, 89 met inclusion. Key immunotherapies included NLRP3 inflammasome inhibitors, regulatory T-cell modulators, and mTOR-targeted agents, which improved re-epithelialization and reduced cytokines in preclinical models. However, evidence in elderly human cohorts was scarce. Adjunctive strategies—such as protein supplementation, senescence-targeted agents, and engineered biomaterials—enhanced immunotherapy effects. Major barriers were the lack of wound-specific formulations, limited geriatric trial representation, and underdeveloped topical delivery systems. While immunotherapy shows mechanistic potential to correct immune dysregulation in chronic wounds, most data remain preclinical. Multi-modal strategies integrating immunotherapy, nutrition, and bioengineered scaffolds, tailored to aging physiology, are needed to improve outcomes and require rigorous clinical validation.

Keywords: Immunotherapy; Chronic Wounds; Aging; Immunosenescence; Inflammasome; Wound Healing; Scoping Review

1. Introduction

Wound management in the elderly poses significant clinical challenges due to physiological changes associated with aging that impair the healing process. These changes include prolonged and dysregulated inflammation, reduced cellular proliferation, delayed epithelialization, and diminished collagen synthesis, all of which contribute to the development and persistence of chronic wounds [1,2]. In particular, the aging immune system—characterized

by immunosenescence—plays a key role in impairing wound resolution and increasing susceptibility to infection. The burden of chronic wounds among older adults is well-documented: in German nursing homes, for example, 7.8% of residents aged 60 years and older suffer from chronic wounds. Pressure ulcers account for the largest proportion (4.0%), followed by ischemic ulcers due to peripheral arterial disease and diabetic foot ulcers, both of which are linked to reduced perfusion and neuropathic complications [1]. These conditions are frequently compounded by comorbidities, such as diabetes mellitus, cardiovascular disease, and cognitive impairment, as well as external risk factors like immobility, poor nutritional status, and polypharmacy [2].

Chronic wounds not only lead to prolonged morbidity but also impose a considerable economic and psychosocial burden [3]. Recurrent wound infections, extended hospitalization, and long-term care costs strain both patients and healthcare systems. Furthermore, the presence of chronic wounds has been associated with significant reductions in quality of life, owing to pain, restricted mobility, social isolation, and emotional distress. In resource-limited or institutional care settings, such as long-term care facilities, these burdens are often exacerbated by staffing limitations and delayed access to wound specialists.

Optimal wound dressing selection is fundamental to effective wound management in the elderly. Traditional dressings, particularly those using strong adhesives, are often associated with medical adhesive-related skin injuries (MARSI)—a condition exacerbated by the fragility and reduced tensile strength of aging skin [4]. Advanced wound dressings have been developed to address these limitations and improve clinical outcomes. Hydrogel dressings, for instance, help maintain a moist wound environment, support autolytic debridement, and enhance transdermal drug delivery. Foam dressings, by contrast, provide superior exudate absorption, cushioning, and microbial barrier protection, making them suitable for moderate to heavily exuding wounds [5]. However, despite advances in dressing technologies, the underlying pathophysiological barriers to wound healing in the elderly often necessitate more than local care—prompting growing interest in systemic approaches, including immunomodulation, nutritional support, and cellular therapy.

Given the complexity and multidimensional nature of chronic wounds in the aging population, there is an urgent need for comprehensive management strategies that extend beyond topical treatment alone. This scoping review aims to synthesize the current understanding of chronic wound epidemiology, underlying biological mechanisms, and evidence-based management strategies in the elderly. By mapping the current evidence landscape, this review seeks to support both clinical decision-making and healthcare policy, with the ultimate goal of improving healing outcomes, reducing complications, and enhancing quality of life in this vulnerable group.

2. Method

This scoping review was conducted following the methodological framework established by Arksey and O'Malley, with enhancements drawn from the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines to ensure systematic rigor, transparency, and internal validity. The aim was to comprehensively map the current body of evidence regarding immunotherapeutic strategies for managing chronic wounds in aging populations, without restricting the analysis to any single intervention type or study design. The review protocol was designed to address clearly defined research questions, including: (1) What immune-related mechanisms contribute to impaired wound healing in elderly individuals? (2) What immunomodulatory or immune-targeted therapies have been studied in preclinical or clinical settings for this population? and (3) What are the reported outcomes, delivery systems, and limitations associated with these strategies?

Eligibility criteria were developed using the Population–Concept–Context (PCC) framework, a recommended approach for scoping reviews. The population of interest was elderly individuals (typically aged ≥ 60 years) presenting with chronic wounds, including pressure ulcers, venous leg ulcers, and diabetic foot ulcers. The central concept focused on immunotherapy, encompassing pharmacological agents (e.g., cytokine inhibitors, immune checkpoint modulators), cell-based therapies (e.g., regulatory T cells, macrophage reprogramming), and supportive strategies targeting immune pathways. The context included both clinical and experimental studies in any healthcare or laboratory setting, without geographic restriction.

A comprehensive literature search was performed across three major electronic databases: PubMed, Scopus, and Web of Science, covering publications from January 2000 to March 2025. Search terms were developed in consultation with a health sciences librarian and combined MeSH terms and keywords related to chronic wounds, aging, and immunotherapy. Additional records were identified by manually screening reference lists of relevant

reviews and included studies.

All identified articles were imported into a reference management system, and duplicates were removed prior to screening. Two independent reviewers conducted a three-stage screening process (title, abstract, full-text) using predefined inclusion and exclusion criteria. Any disagreements were resolved by consensus, and a third reviewer was available for adjudication if needed. A standardized data charting form was developed and pilot-tested to ensure consistent extraction of information, including study design, wound type, population characteristics, immunological targets, intervention types, outcome measures, and main findings.

While formal risk of bias assessments are not required in scoping reviews, the included studies were examined narratively for methodological adequacy, clarity of immunological targeting, and relevance to elderly populations. Studies were not excluded based on quality but were contextualized accordingly in the synthesis to prevent overinterpretation of preliminary or exploratory data. Potential limitations, including publication bias, heterogeneity in intervention definitions, and variation in outcome reporting, were documented. This methodological approach maximizes internal validity by employing transparent and reproducible processes in literature identification, data abstraction, and interpretation. The findings offer a foundational evidence map that can inform future systematic reviews, meta-analyses, or hypothesis-driven clinical trials focused on immunomodulatory wound care strategies in aging populations.

3. The Biology of Wound Healing

Wound healing is a complex, dynamic process that occurs in four overlapping but distinct stages: hemostasis, inflammation, proliferation, and maturation. Each phase is regulated by a coordinated cascade of cellular and molecular events that restore skin integrity. The process begins with hemostasis, which occurs immediately after injury and serves to prevent further blood loss. Platelets aggregate at the wound site and initiate clot formation through the coagulation cascade, simultaneously releasing pro-inflammatory cytokines and growth factors that initiate downstream healing responses. Following clot stabilization, the inflammatory phase is triggered within hours. Neutrophils are among the first immune cells to infiltrate the site, where they are responsible for clearing debris and microbial contaminants. They are later replaced by macrophages, which play a dual role in host defense and in orchestrating the transition to the proliferative phase through the release of cytokines such as TGF-β and VEGF. These mediators recruit and activate keratinocytes, fibroblasts, and endothelial cells to initiate tissue regeneration.

The proliferative phase is characterized by re-epithelialization, angiogenesis, and the synthesis of extracellular matrix (ECM). Fibroblasts migrate into the wound bed and produce type III collagen and glycosaminoglycans, laying the groundwork for new tissue. Concurrently, endothelial cells form new capillaries to ensure the supply of oxygen and nutrients, while myofibroblasts contribute to wound contraction, thereby reducing the wound size. In the final maturation or remodeling phase, type III collagen is gradually replaced by stronger, cross-linked type I collagen, improving tensile strength. This phase also involves the resolution of inflammation, apoptosis of excess cells (e.g., fibroblasts and endothelial cells), and reorganization of the ECM. The process may take weeks to months and is essential for achieving stable wound closure and restoring skin function [6]. An emerging area of interest in wound biology is the role of epidermal autophagy, a catabolic process critical for maintaining keratinocyte homeostasis and coordinating immune–epithelial communication. Autophagy facilitates the clearance of damaged organelles and supports cellular stress adaptation, enabling keratinocytes to proliferate and migrate efficiently during wound healing. Experimental models have demonstrated that inhibiting autophagy impairs wound closure, disrupts epithelial barrier regeneration, and alters local cytokine signaling. Specifically, impaired autophagy reduces the production of CCL2, a chemokine essential for recruiting and activating fibroblasts [7]. This disruption compromises fibroblast-mediated matrix deposition and angiogenesis, further delaying healing. However, exogenous administration of recombinant CCL2 has been shown to partially rescue healing deficits in autophagy-deficient models, underscoring the importance of this chemokine as a downstream effector of epithelial immune crosstalk. These findings suggest that therapeutic modulation of autophagy or CCL2 signaling may hold promise for enhancing wound healing, particularly in populations with impaired epithelial regenerative capacity, such as the elderly. Together, these biological insights underscore the multifaceted and finely regulated nature of wound healing, providing mechanistic targets for the development of novel therapies that aim to improve outcomes in chronic or age-related wounds (as shown in **Figure 1**).

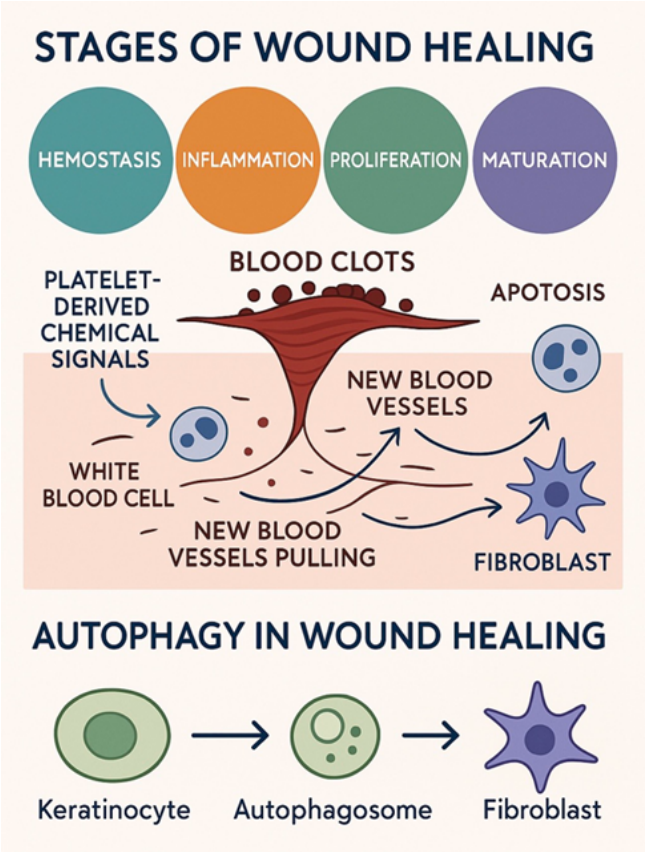

Figure 1. Biology of wound healing.

Note: Wound healing occurs in four overlapping phases: hemostasis (clot formation), inflammation (removal of debris), proliferation (tissue regeneration), and maturation (tissue strengthening). This figure shows that epidermal autophagy plays a key role by regulating keratinocyte activity, fibroblast communication, and CCL2 signaling for effective skin repair.

4. Cellular Dysregulation in Aging Skin

4.1. Structural and Functional Changes in Aging Skin

Aging skin experiences structural and biochemical changes that impair wound healing, primarily due to the decline in dermal fibroblast function and reduced collagen and ECM production, leading to skin thinning and delayed repair. Senescent fibroblasts exacerbate this by disrupting ECM remodeling [7]. The ECM becomes disorganized, with misaligned collagen, fragmented elastin, and reduced glycoproteins, which contribute to poor angiogenesis and chronic wounds in the elderly [8]. Additionally, elevated matrix metalloproteinases (MMPs) degrade ECM and angiogenic factors, impairing keratinocyte migration and tissue regeneration [7,8].

4.2. Immunosenescence and Inflammatory Imbalance

Aging impairs immune function through immunosenescence and chronic low-grade inflammation (inflammaging), driven by telomere shortening, mitochondrial dysfunction, oxidative stress, and lifelong antigen exposure, all of which weaken skin repair and defense [9]. Neutrophils in the elderly exhibit prolonged activation and excessive NET formation, contributing to tissue damage and delayed healing [10]. Aging macrophages show reduced phagocytosis and heightened pro-inflammatory activity, further impairing tissue repair [11]. Additionally, chronic NLRP3 inflammasome activation elevates IL-1β and IL-18 levels, promoting systemic inflammation and age-related diseases [12].

4.3. Delayed Reepithelialization and Angiogenesis

Chronic wound healing in the elderly is marked by delayed reepithelialization and impaired angiogenesis. Keratinocytes, which are essential for wound closure, become dysfunctional with age, leading to the overexpression

of Toll-like receptors and sustained inflammation. This persistent inflammatory state increases matrix metalloproteinase (MMP) activity, which degrades the extracellular matrix and inhibits keratinocyte migration, thereby stalling epithelial repair [13]. At the same time, angiogenesis is compromised due to reduced expression of VEGF-A and diminished signaling through VEGFR-2, which impairs new blood vessel formation and oxygen delivery to the wound [14]. Innovative therapies such as VEGF delivery systems, growth factor-infused dressings, and hyaluronic acid-based hydrogels are being developed to counteract these deficits. Hyaluronic acid is especially promising due to its ability to maintain tissue hydration, support cell migration, and mimic the extracellular matrix [15].

5. Nutritional Impact on Wound Healing in Older Adults

5.1. Nutrient Deficiencies and Wound Repair

Protein is essential for wound healing, as it supports collagen synthesis, angiogenesis, and fibroblast proliferation. Deficiencies hinder immunity and delay repair, while amino acids such as arginine and glutamine aid healing by enhancing immune response, nitric oxide production, and antioxidant activity [16]. Micronutrients are also vital: zinc aids in re-epithelialization and immune function, vitamin C supports collagen synthesis and immune defense, and vitamin A promotes epithelial growth and fibroblast activity while mitigating the effects of corticosteroid on repair [16]. Essential fatty acids, particularly omega-3s, help regulate inflammation and stabilize cell membranes; however, excessive early intake may impair immunity and delay healing, highlighting the importance of timing and dosage [16]. Chronic catabolic conditions like cachexia divert nutrients to acute-phase responses, limiting availability for tissue repair. Muscle-derived proteins and appetite-suppressing agents, such as lipocalin, further drive nutrient depletion [17]. Sarcopenia, often underrecognized due to diagnostic challenges, contributes to poor healing through loss of muscle mass and function, which are critical for immune and repair processes. Addressing sarcopenia, frailty, and inactivity is essential for comprehensive wound care [18].

5.2. Albumin as a Prognostic Marker

Hypoalbuminemia is a strong predictor of poor wound healing and heightened infection risk in surgical patients, reflecting underlying malnutrition, inflammation, and physiological stress. Clinically, it is linked to higher rates of surgical site infections, wound dehiscence, and sepsis. For instance, albumin levels under 3.3 g/dL in head and neck cancer surgeries tripled the risk of SSIs, while levels below 2.5 g/dL after oral cancer surgery predicted infections by day 10 [19]. Mechanistically, low albumin levels reduce oncotic pressure, leading to tissue edema, poor oxygenation, and compromised nutrient delivery. Albumin also contributes amino acids for tissue repair, acts as a carrier for essential molecules, and provides antioxidant and anti-inflammatory support [19]. In diabetic foot ulcers, preoperative albumin levels under 3.5 g/dL increased the risk of nonhealing at 28 days, with 3.44 g/dL identified as the optimal predictive threshold (AUC = 0.727) [20]. In summary, hypoalbuminemia is a modifiable factor, and its management may enhance wound healing and surgical outcomes.

5.3. Nutritional Interventions and Supplementation

Nutritional support is essential for effective wound healing, as malnutrition is associated with an increased risk of postoperative complications, including delayed healing, higher infection rates, and prolonged hospital stays. Preoperative nutritional optimization, a key component of ERAS protocols, helps mitigate these risks. Enteral nutrition is generally preferred over parenteral feeding due to its physiological benefits, including maintaining gut integrity and lowering the risk of infections and impaired healing. However, when enteral feeding is not possible, such as after sacrectomy, parenteral nutrition (including TPN) can improve healing outcomes, metabolic status, and reduce hospitalization duration, despite a higher risk of complications [16,21]. In elderly patients, age-related metabolic changes impair wound healing by shifting skin cell metabolism toward glycolysis, reducing ATP production, and causing mitochondrial dysfunction (as shown in **Figure 2**). This limits the energy required for key healing processes, such as cell proliferation and tissue remodeling, highlighting the importance of improving mitochondrial function and ATP synthesis in aged skin [22,23]. Protein supplementation is also vital, as it provides essential amino acids for collagen synthesis, angiogenesis, and fibroblast activity. Arginine enhances nitric oxide production and blood vessel formation, while glutamine supports immune function and antioxidant defense. Protein deficiency can significantly hinder healing, whereas supplementation reduces postoperative complications, particularly in pa-

tients undergoing plastic surgery and those who have undergone bariatric surgery [16].

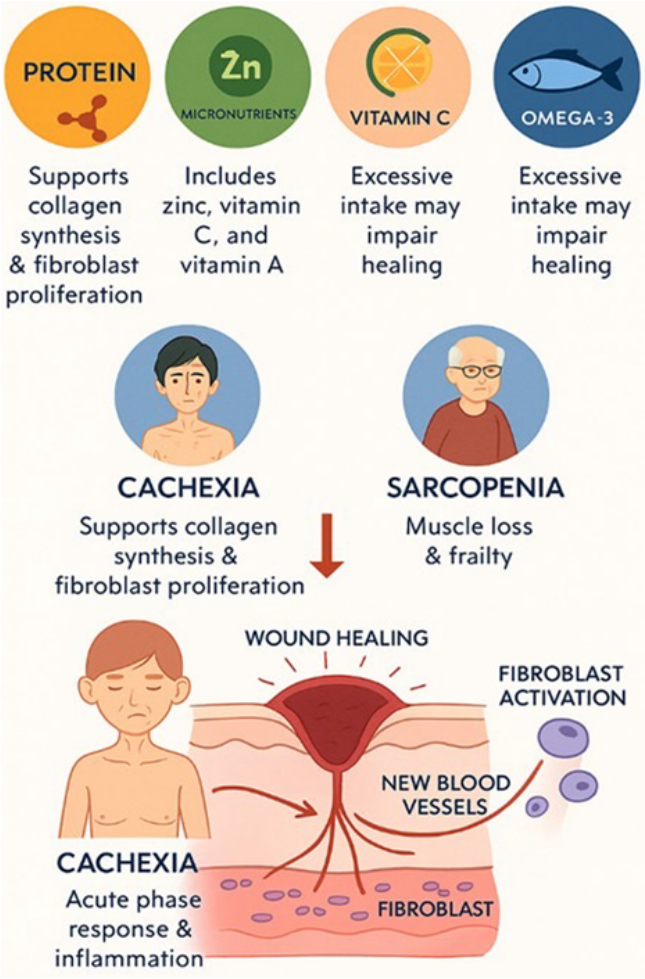

Figure 2. Nutritional factors and their impact on wound healing in older adults.

Note: This figure summarizes the critical nutrients (key nutrients such as protein, amino acids, zinc, vitamins A and C, essential fatty acids, and albumin) and metabolic factors that influence wound healing in older adults. Malnutrition-related conditions such as cachexia and sarcopenia hinder healing by causing inflammation and nutrient loss. Targeted nutritional support is crucial to improve healing outcomes in the elderly.

5.4. Clinical Challenges in Geriatric Wound Care

Chronic wound management in older adults is challenged by comorbidities like diabetes, vascular disease, renal insufficiency, and heart conditions, which impair healing through mechanisms such as chronic inflammation, ischemia, and cellular dysfunction (as shown in **Figure 3**). These conditions promote senescence in key reparative cells, such as fibroblasts and keratinocytes, thereby limiting tissue regeneration. Some drugs can further delay healing by suppressing critical physiological processes. Aging also results in structural skin changes, including thinning of the epidermis, reduced elasticity, and decreased collagen, making the skin more vulnerable to trauma—especially from adhesive dressings [24]. Silicone-based and moisture-retentive dressings, such as hydrogels and foam dressings, help minimize tissue damage and support healing in chronic wounds by maintaining a moist environment and reducing trauma during dressing changes [5]. Biofilms, found in up to 60% of chronic wounds, are a major barrier to healing due to their role in sustaining inflammation and resisting treatment. Pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* commonly form biofilms [25]. Silver-containing dressings offer broad-spectrum antimicrobial activity but raise concerns about cytotoxicity and potential harm to beneficial bacteria, necessitating careful consideration in their use (as shown in **Table 1**) [5].

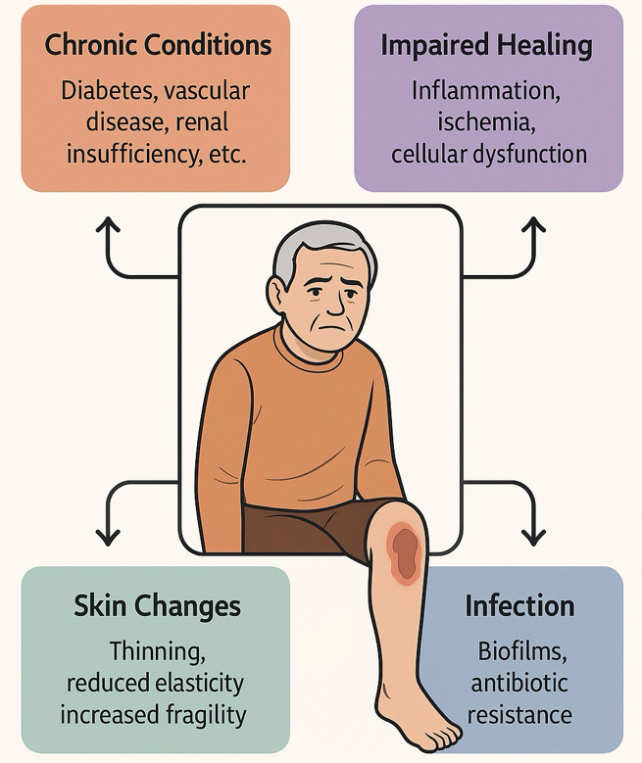

Figure 3. Factors contributing to wound formation in the elderly.

Note: This figure shows key factors that contribute to poor wound healing in elderly patients. These include chronic conditions, impaired healing due to inflammation and cell dysfunction, skin changes, and infections that may involve antibiotic resistance. These factors are interconnected, making wound recovery more challenging.

Table 1. Comparison of traditional vs modern dressings.

Comparison Aspect	Traditional Wound Dressings	Modern Wound Dressings
Material	Gauze, cotton wool, bandages	Hydrocolloids, alginates, foams, hydrogels, films
Moisture Control	Poor moisture control	Good moisture control, promotes faster healing
Fluid Absorption	Moderate absorption	Excellent exudate absorption, reduces infection risk
Dressing Change Frequency	Frequent changes may cause trauma	Less frequently, minimizes wound disturbance
Antimicrobial Properties	None or minimal	Some have antimicrobial agents (e.g., silver, iodine)
Cost	Low	Higher than traditional dressings
Overall Effectiveness	Basic protection	High effectiveness in healing and reducing complications

Note: Table summarizes the comparison between traditional and modern wound dressings across various aspects, such as material, moisture control, absorption, antimicrobial properties, and overall effectiveness.

5.5. Advances in Dressing Technologies and Topical Therapies

According to **Table 1**, hydrocolloid dressings contain hydrophilic colloids such as gelatin, pectin, and carboxymethylcellulose that form a gel upon contact with wound exudate, supporting autolytic debridement and maintaining a moist healing environment. They are semi-occlusive, allowing gas exchange while blocking bacteria, and are best suited for low to moderate exuding wounds, although not suitable for heavily exuding or infected wounds due to the risks of maceration and anaerobic growth [26]. Foam dressings, usually made from polyurethane, are ideal for moderate to heavily exuding wounds due to their high absorbency, flexibility, and ability to retain moisture. Their 3D structure suits deeper wounds, and some are enhanced with antimicrobial agents, such as silver or zinc oxide nanoparticles [5]. Silver-impregnated dressings, especially those containing silver nanoparticles (Ag-NPs), provide broad-spectrum antimicrobial action, making them effective for treating chronic and infected wounds, such as diabetic ulcers. Silver acts by damaging microbial membranes, inducing oxidative stress, and interfering with DNA, thereby promoting healing without significant topical toxicity [27]. Soft silicone gel-based dressings are noted for their gentle adhesion, flexibility, and ability to maintain a moist wound environment, supporting healing while minimizing skin damage [5]. In resource-limited settings, soft gauze with moisturizers can be an effective

option, supported by caregiver education in wound care. Saline or warm tap water is suitable for cleansing, and severe wounds should be referred for advanced care. Skin tears should be managed by realigning skin flaps and using non-adherent dressings, such as Cuticerin under Melolin, with dressings extending 2 cm beyond the wound edges and directional arrows marked to aid in an atraumatic approach, well-suited to home care [28]. **Figure 4** demonstrates the selection of a wound dressing.

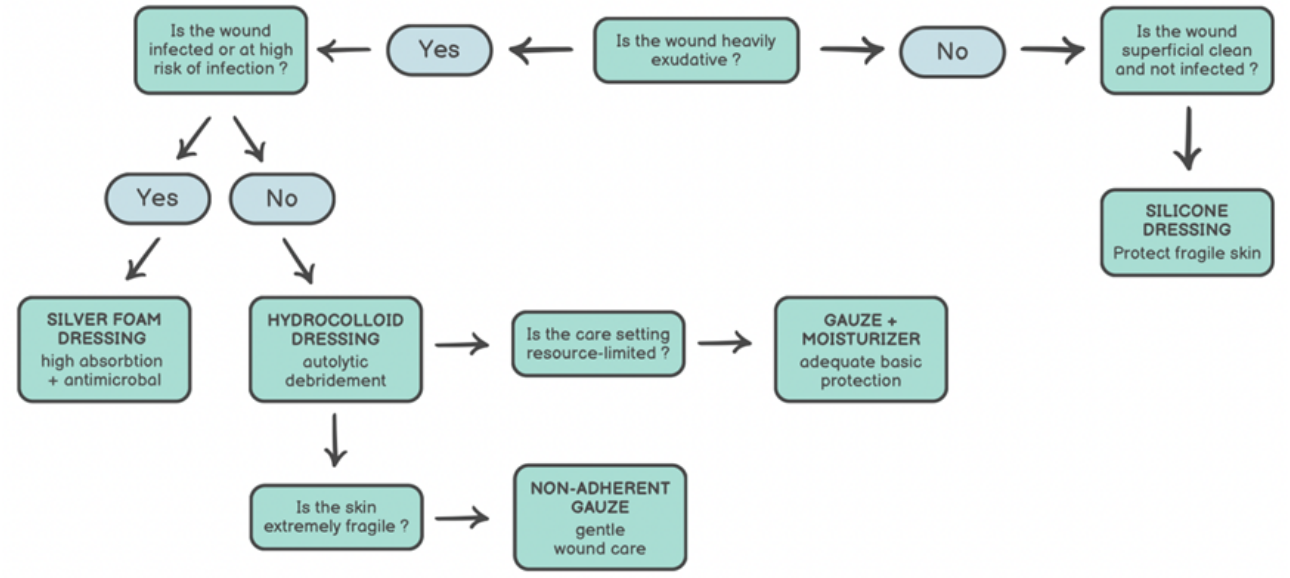

Figure 4. Selection of a wound dressing.

Note: This figure illustrates a structured wound care process: detect the wound, utilize telemedicine for communication, select advanced dressings, create a personalized plan, monitor progress, provide feedback to the care team, and adjust the plan as needed.

6. Health System Barriers and Solutions

6.1. Barriers to Optimal Care

Despite advances in wound care science, systemic barriers persist in limiting the delivery of optimal care to aging populations. Limited access to advanced wound products—including hydrogels, foams, and antimicrobial dressing remains a critical challenge, particularly in low-resource or long-term care settings. Cost-related issues, including insufficient insurance coverage and geographic disparities, further widen the gap in access to high-quality interventions [28]. Additionally, variations in clinician knowledge, training, and adherence to evidence-based wound care guidelines contribute to inconsistent care delivery and suboptimal outcomes for elderly patients [3].

6.2. Innovations in Care Delivery

Innovative care models are emerging to address these barriers. Telemedicine offers a practical solution for follow-up care, especially in remote or mobility-limited populations, enabling timely assessment and early intervention [29]. Community health workers and mobile wound care outreach teams are used to extend services into underserved areas [28]. Furthermore, subsidized wound care programs, home-based services, and structured patient education initiatives have demonstrated promise in improving self-management and reducing wound-related complications [3,30]. The examples of chronic wound care workflow are shown in **Figure 5**.

6.3. Immune-Targeted Therapies in Aging Wound Healing

With advancing age, the wound healing process becomes increasingly compromised due to immunosenescence and a persistent low-grade inflammatory state commonly referred to as "inflammaging." In this context, immune-targeted therapies have emerged as promising adjuncts in the management of chronic wounds in older adults.[9,12] Strategies aimed at modulating key components of the innate immune system—particularly macrophage and neutrophil function, as well as inflammasome activity—have shown potential in correcting the dysregulated

inflammatory responses that characterize non-healing wounds.[10,11] Among these, the NLRP3 inflammasome has garnered particular interest due to its pivotal role in driving the overproduction of IL-1β and IL-18, leading to sustained neutrophilic infiltration, extracellular matrix degradation, and impaired tissue regeneration. These effects are exacerbated in aging skin, where baseline inflammatory signaling is already elevated. Targeting NLRP3 with selective inhibitors such as MCC950 has demonstrated encouraging results in preclinical settings. In a murine model of delayed wound healing, treatment with MCC950 resulted in a 42% increase in wound closure by day 10 compared to untreated controls ($p < 0.01$), alongside marked reductions in IL-1β and IL-18 levels.[12] Histological assessments further confirmed enhanced granulation tissue and decreased inflammatory cell infiltration. Beyond pharmacologic agents, immunomodulatory cell-based strategies are also gaining traction. Regulatory T cells (Tregs), which play a key role in resolving inflammation and supporting tissue repair, have been shown to decline functionally with age. In aged mice, the adoptive transfer of $CD4^+Foxp3^+$ Tregs significantly improved re-epithelialization by 35% compared to non-treated aged controls ($p = 0.03$), correlating with increased amphiregulin expression and suppression of pro-inflammatory cytokines, such as TNF-α and CXCL1 [17]. These findings underscore the mechanistic and therapeutic relevance of immune modulation in age-impaired wound healing and highlight the need for translational research to validate these interventions in human subjects.

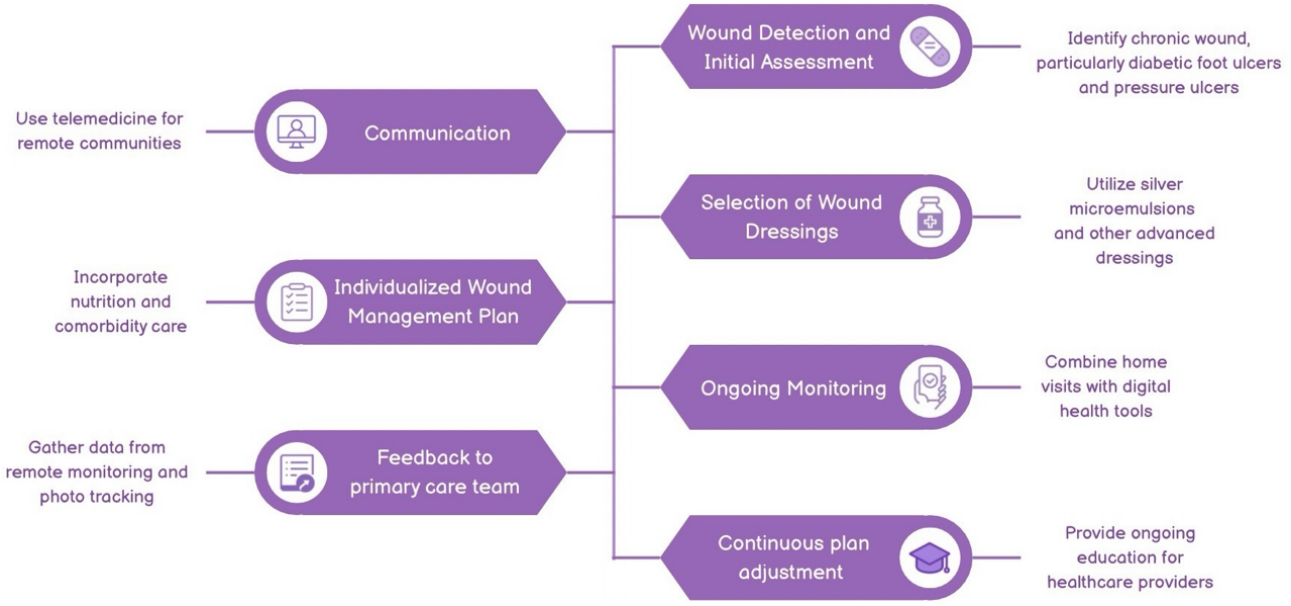

Figure 5. Chronic wound care workflow.

Note: This image illustrates a step-by-step plan for chronic wound care utilizing telemedicine, advanced dressings, regular monitoring, and ongoing updates to enhance treatment.

Furthermore, biologics such as IL-1 receptor antagonists (e.g., anakinra) may mitigate excessive inflammatory signaling and accelerate healing in inflamed or non-healing wounds [12]. In parallel, enhancing regulatory T-cell (Treg) function and utilizing mesenchymal stem cell (MSC)-derived exosomes have demonstrated immunomodulatory effects, thereby promoting a regenerative wound environment [22]. Advances in nanocarrier-based delivery systems also facilitate the localized and sustained release of these immunotherapeutics, minimizing systemic side effects [6]. While these therapies are still largely experimental, their targeted nature holds promise for restoring immune balance and improving wound resolution in elderly patients with chronic non-healing wounds [12,22].

6.4. Immune-Targeted Therapies and Marketed Agents in Aging Wound Healing

In the context of chronic wounds complicated by immunosenescence and sustained inflammation [9], several marketed immunomodulatory agents have shown promise—either directly or through repurposing—for enhancing wound healing. For instance, anakinra, an interleukin-1 receptor antagonist approved for the treatment of rheumatoid arthritis, has been studied for off-label use in modulating IL-1β-mediated inflammation in chronic wounds [12]. Tacrolimus, a calcineurin inhibitor used in atopic dermatitis, has demonstrated topical efficacy in

reducing local inflammation and promoting re-epithelialization in chronic dermatoses [13]. Colchicine, traditionally used in gout, inhibits the NLRP3 inflammasome and may reduce sustained inflammation in chronic skin injuries [12]. In cases of neutrophil-mediated tissue damage, dapsone—an anti-inflammatory and antimicrobial agent—has been used both topically and systemically in dermatologic ulcerations [10]. Furthermore, sirolimus (rapamycin), an mTOR inhibitor used in transplant medicine, has shown potential to enhance autophagy and promote skin regeneration in elderly or immunocompromised individuals [22]. While none of these agents are currently approved specifically for wound healing, their immunomodulatory mechanisms suggest clinical utility in select chronic wound scenarios. Emerging delivery platforms, such as hydrogels and controlled-release nanocarriers, may enhance safety and local bioavailability, especially in geriatric populations [6,27].

Although a variety of immunomodulatory agents—including NLRP3 inhibitors, IL-1 antagonists, and mTOR inhibitors such as sirolimus—have demonstrated therapeutic potential in chronic wound healing, the article acknowledges the need for more precise differentiation between universally applicable strategies and those tailored explicitly to aging-associated impairments [12]. Chronic wounds in older adults are uniquely characterized by immunosenescence, mitochondrial dysfunction, and a decline in autophagic activity, which collectively disrupt normal tissue repair. Sirolimus, through its inhibition of mTOR, promotes autophagy and reduces inflammatory signaling—mechanisms relevant across age groups—but mounting evidence suggests its effect is particularly pronounced in aged tissue [12]. Preclinical studies in senescent murine models have shown that sirolimus significantly enhances re-epithelialization, granulation tissue formation, and collagen remodeling in aged wounds, whereas the impact is comparatively modest in younger counterparts where basal autophagic flux remains intact [31]. These findings underscore sirolimus's potential as an aging-specific intervention that corrects dysregulated pathways less evident in younger hosts. However, while experimental data support this mechanistic plausibility, further age-stratified clinical trials are essential to establish the differential efficacy of sirolimus and similar agents in human populations and to refine therapeutic strategies accordingly.

7. Limitations of Immune-Targeted Therapies in Geriatric Wound Care

Although immunomodulatory therapies represent a promising avenue for managing chronic wounds in older adults, their clinical application remains constrained by several significant challenges. Systemic agents such as anakinra, tacrolimus, and sirolimus may pose immunosuppressive risks, potentially increasing susceptibility to infection, impairing pathogen clearance, or elevating the risk of malignancy—concerns that are particularly relevant in immunosenescent populations. Furthermore, age-related alterations in drug metabolism and renal or hepatic clearance complicate dosing strategies and may elevate the risk of adverse drug events. Most approved immunomodulatory agents have not been evaluated explicitly for chronic wound indications, especially in elderly cohorts, and current use in this context is often extrapolated from preclinical or anecdotal evidence rather than from wound-specific clinical trials. Additionally, the pathophysiology of chronic wounds in older adults is inherently multifactorial, often involving persistent biofilm, ischemic microenvironments, and nutritional deficiencies—factors that cannot be adequately addressed by immune modulation alone. The development and accessibility of topical delivery systems for immunotherapeutics also remain limited, and adherence may be suboptimal in community or home-care settings. Cost and reimbursement barriers for biologics further limit their practical utility in routine geriatric care. Importantly, coexisting malnutrition, particularly hypoalbuminemia—has a significant impact on immune function and tissue regeneration. Protein-energy malnutrition and micronutrient deficiencies can impair leukocyte activity, blunt cytokine signaling, and delay collagen synthesis. Therefore, integrating targeted nutritional support alongside immunomodulatory treatment is not merely supportive but essential to improving wound healing outcomes in older adults. A comprehensive, multimodal approach that aligns pharmacologic strategies with metabolic and functional needs is likely to yield the most clinically meaningful benefits.

8. Future and Innovations

As the global population continues to age, the clinical burden of chronic wounds in elderly individuals is expected to escalate, necessitating the development of more effective, targeted, and accessible therapeutic innovations. While current standard treatments emphasize wound dressings, infection control, and metabolic management, these modalities often fall short in addressing the immunological and regenerative deficits associated with

aging[10,24]. Future directions in geriatric wound care are therefore moving toward integrative approaches that modulate underlying biological dysfunctions, particularly those related to immunosenescence, inflammation, and tissue regeneration[9,12]. Among the most promising innovations are immune-targeted therapies, bioengineered cell-based treatments, and personalized care strategies leveraging digital health technologies[29,30].

A major area of advancement lies in targeted immunomodulation, which seeks to recalibrate the aberrant immune responses seen in elderly wounds. Novel agents such as NLRP3 inflammasome inhibitors (e.g., MCC950) and IL-1β antagonists (e.g., anakinra) are under investigation for their capacity to reduce chronic inflammation, promote resolution, and restore macrophage function[12]. Experimental models have shown these agents significantly enhance wound closure and reduce inflammatory cytokine expression[12]. Similarly, regulatory T cell (Treg)-based therapies have demonstrated potential in reversing age-related immune dysfunction. Adoptive transfer of Tregs in preclinical studies has resulted in improved epithelialization, matrix remodeling, and reduced fibrosis in aged mice[17]. While these approaches are promising, translational challenges include immune tolerance, dosing precision, and safety profiles in comorbid elderly patients[9].

The intersection of immunotherapy and biomaterials is another frontier in wound care innovation. Topical delivery platforms such as hydrogel-embedded cytokines, scaffold-based immunomodulators, and microneedle patches allow for localized immunological reprogramming without systemic side effects[15]. These delivery systems can be engineered to respond dynamically to wound microenvironment cues—such as pH or reactive oxygen species—enabling smart, controlled release of immune modulators[15,27]. In tandem, advances in wound bioengineering, including the use of decellularized extracellular matrix (ECM) scaffolds, autologous fibroblast sheets, and bioactive peptides, are revolutionizing the support of tissue regeneration in non-healing wounds[6,31].

Another emerging innovation involves the use of genomic and transcriptomic profiling to tailor wound care based on individual biological responses. Precision medicine approaches that stratify patients by inflammatory gene expression signatures, proteomic markers, or senescence-associated profiles may soon allow clinicians to select the most appropriate intervention—whether immunotherapy, growth factors, or stem cell-based therapies—based on a wound's molecular phenotype[9,22]. Technologies such as single-cell RNA sequencing and spatial transcriptomics are beginning to uncover cellular heterogeneity within chronic wounds, shedding light on dysfunctional fibroblast and immune subpopulations that could be therapeutically targeted[9,13].

Stem cell therapies, particularly those involving mesenchymal stem cells (MSCs), continue to hold promise due to their immunoregulatory and pro-regenerative properties[6]. MSCs derived from adipose, or bone marrow sources have been shown to accelerate wound healing by secreting trophic factors, modulating local immune responses, and promoting angiogenesis[6]. In aging populations, however, autologous cell potency may be diminished; thus, allogeneic or induced pluripotent stem cell (iPSC)-derived options are being explored[17].

Concurrently, the role of nutrition and metabolic modulation is gaining recognition as a fundamental component of future wound care models. Nutritional deficits such as hypoalbuminemia, zinc deficiency, and vitamin C insufficiency impair immune cell function and tissue repair, particularly in elderly patients[16,19,20]. Novel interventions integrating protein supplementation, targeted micronutrient therapy, and metabolic enhancers, such as metformin (which may also modulate inflammation and autophagy), are under exploration[22,23].

Digital health innovations such as remote wound monitoring, telehealth consultations, and artificial intelligence–based wound assessment tools are also transforming care delivery[29,30]. Smartphone-enabled imaging and deep learning algorithms can quantify wound size, depth, exudate, and granulation in real-time, providing clinicians with actionable insights while reducing the need for frequent in-person evaluations. These technologies are particularly relevant for aging individuals living in rural or long-term care settings, where access to specialized wound care may be limited[29].

9. Conclusion

Chronic wounds in aging populations arise from a complex interplay of biological aging, immune dysregulation, nutritional deficits, and systemic care limitations. Addressing these challenges requires an integrative approach that combines targeted nutritional support, advanced dressing technologies, and emerging immune-modulating therapies. While innovations such as immune-targeted agents and regenerative materials show promise, their implementation is hindered by limited evidence, safety concerns, and accessibility issues. Moving forward, interdisciplinary collaboration, improved clinician education, and equitable access to care are essential to enhance healing

outcomes and quality of life in older adults.

Author Contributions

K.R. conceptualized the review, conducted the literature search, and led the drafting of the manuscript. P.K. and T.T. (Thanaporn Thakolpattanakul) contributed to data extraction, thematic synthesis, and critical revision of the manuscript. T.T. (Thanakrit Thakolpattanakul) assisted with methodological design and helped ensure consistency with scoping review standards. K.P. supported data verification and reference management. P.P. supervised the entire project, provided senior academic guidance, and served as the corresponding author. All authors have read and approved the final version of the manuscript.

Funding

This work received no external funding.

Institutional Review Board Statement

Ethical reviews and approval were waived for this study, as it involved only the analysis of publicly available literature and did not include any human participants, personal data, or clinical interventions.

Informed Consent Statement

Not applicable. This study was based solely on previously published literature and did not involve human participants or identifiable personal data.

Data Availability Statement

All data supporting the findings of this study are available within the published articles cited in the manuscript. No new data was generated or analyzed by the authors.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Raeder, K.; Jachan, D.E.; Müller-Werdan, U.; et al. Prevalence and Risk Factors of Chronic Wounds in Nursing Homes in Germany: A Cross-Sectional Study. *Int. Wound J.* **2020**, *17*, 1128–1134.
2. Khalid, K.A.; Nawi, A.F.M.; Zulkifli, N.; et al. Aging and Wound Healing of the Skin: A Review of Clinical and Pathophysiological Hallmarks. *Life* **2022**, *12*, 2142.
3. Martinengo, L.; Yeo, N.J.Y.; Tang, Z.Q.; et al. Digital Education for the Management of Chronic Wounds in Health Care Professionals: Protocol for a Systematic Review by the Digital Health Education Collaboration. *JMIR Res. Protoc.* **2019**, *8*, e12488.
4. de Faria, M.F.; Ferreira, M.B.G.; Dos Santos Felix, M.M.; et al. Prevention of Medical Adhesive-Related Skin Injury During Patient Care: A Scoping Review. *Int. J. Nurs. Stud. Adv.* **2022**, *4*, 100078.
5. Alberts, A.; Tudorache, D.I.; Niculescu, A.G.; et al. Advancements in Wound Dressing Materials: Highlighting Recent Progress in Hydrogels, Foams, and Antimicrobial Dressings. *Gels* **2025**, *11*, 123.
6. Sangnim, T.; Puri, V.; Dheer, D.; et al. Nanomaterials in the Wound Healing Process: New Insights and Advancements. *Pharmaceutics* **2024**, *16*, 300.
7. Qiang, L.; Yang, S.; Cui, Y.H.; et al. Keratinocyte Autophagy Enables the Activation of Keratinocytes and Fibroblasts and Facilitates Wound Healing. *Autophagy* **2021**, *17*, 2128–2143.
8. Mavrogonatou, E.; Papadopoulou, A.; Pratsinis, H.; et al. Senescence-Associated Alterations in the Extracellular Matrix: Deciphering Their Role in the Regulation of Cellular Function. *Am. J. Physiol. Cell Physiol.* **2023**, *325*, C633–C647.
9. Pająk, J.; Nowicka, D.; Szepietowski, J.C. Inflammaging and Immunosenescence as Part of Skin Aging—A Narrative Review. *Int. J. Mol. Sci.* **2023**, *24*, 7784.

10. Wang, H.; Kim, S.J.; Lei, Y.; et al. Neutrophil Extracellular Traps in Homeostasis and Disease. *Signal Transduct. Target. Ther.* **2024**, *9*, 235.
11. Lee, M.; Du, H.; Winer, D.A.; et al. Mechanosensing in Macrophages and Dendritic Cells in Steady-State and Disease. *Front. Cell Dev. Biol.* **2022**, *10*, 1044729.
12. Meyers, A.K.; Zhu, X. The NLRP3 Inflammasome: Metabolic Regulation and Contribution to Inflammaging. *Cells* **2020**, *9*, 1808.
13. Piipponen, M.; Li, D.; Landén, N.X. The Immune Functions of Keratinocytes in Skin Wound Healing. *Int. J. Mol. Sci.* **2020**, *21*, 8790.
14. Melincovici, C.S.; Boşca, A.B.; Şuşman, S.; et al. Vascular Endothelial Growth Factor (VEGF)—Key Factor in Normal and Pathological Angiogenesis. *Rom. J. Morphol. Embryol.* **2018**, *59*, 455–467.
15. Gholamali, I.; Vu, T.T.; Jo, S.H.; et al. Exploring the Progress of Hyaluronic Acid Hydrogels: Synthesis, Characteristics, and Wide-Ranging Applications. *Materials* **2024**, *17*, 2439.
16. Seth, I.; Lim, B.; Cevik, J.; et al. Impact of Nutrition on Skin Wound Healing and Aesthetic Outcomes: A Comprehensive Narrative Review. *JPRAS Open* **2024**, *39*, 291–302.
17. Robinson, T.P.; Hamidi, T.; Counts, B.; et al. The Impact of Inflammation and Acute Phase Activation in Cancer Cachexia. *Front. Immunol.* **2023**, *14*, 1207746.
18. Gomes, T.; Trombini, K.C.B.; Martins, M.V.S.; et al. Screening for Sarcopenia and Frailty in Patients With Chronic Venous Ulcers: A Cross-Sectional Study. *J. Vasc. Bras.* **2020**, *19*, 54.
19. Wiedermann, C.J. Hypoalbuminemia as Surrogate and Culprit of Infections. *Int. J. Mol. Sci.* **2021**, *22*, 4496.
20. Satriadinatha, G.B.Y.; Darwis, P.; Hutauruk, P.M.S.; et al. Serum Albumin Levels as Predictors of Microvascular Health and Wound Healing Outcomes in Diabetic Foot Ulcers. *J. Angiother.* **2024**, *8*, 1–8.
21. Gao, S.; Zheng, Y.; Liu, X.; et al. Effect of Early Fasting and Total Parenteral Nutrition Support on the Healing of Incision and Nutritional Status in Patients After Sacrectomy. *Orthop. Traumatol. Surg. Res.* **2018**, *104*, 539–544.
22. Zhuang, Y.; Jiang, S.; Deng, X.; et al. Energy Metabolism as Therapeutic Target for Aged Wound Repair by Engineered Extracellular Vesicle. *Sci. Adv.* **2024**, *10*, 1–16.
23. Vinaik, R.; Barayan, D.; Auger, C.; et al. Regulation of Glycolysis and the Warburg Effect in Wound Healing. *JCI Insight* **2020**, *5*, e138949.
24. Frykberg, R.G.; Banks, J. Challenges in the Treatment of Chronic Wounds. *Adv. Wound Care (New Rochelle)* **2015**, *4*, 560–582.
25. Goswami, A.G.; Basu, S.; Banerjee, T.; et al. Biofilm and Wound Healing: From Bench to Bedside. *Eur. J. Med. Res.* **2023**, *28*, 157.
26. Kamińska, M.S.; Cybulska, A.M.; Skonieczna-Żydecka, K.; et al. Effectiveness of Hydrocolloid Dressings for Treating Pressure Ulcers in Adult Patients: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2020**, *17*, 7881.
27. Rybka, M.; Mazurek, Ł.; Konop, M. Beneficial Effect of Wound Dressings Containing Silver and Silver Nanoparticles in Wound Healing—From Experimental Studies to Clinical Practice. *Life* **2022**, *13*, 69.
28. Beechey, R.; Priest, L.; Peters, M.; et al. An Evidence-Based Approach to the Prevention and Initial Management of Skin Tears Within the Aged Community Setting: A Best Practice Implementation Project. *JBI Database Syst. Rev. Implement. Rep.* **2015**, *13*, 421–443.
29. Chen, L.; Cheng, L.; Gao, W.; et al. Telemedicine in Chronic Wound Management: Systematic Review and Meta-Analysis. *JMIR MHealth UHealth* **2020**, *8*, e15574.
30. Mohammed, H.T.; Corcoran, K.; Lavergne, K.; et al. Clinical, Operational, and Economic Benefits of a Digitally Enabled Wound Care Program in Home Health: Quasi-Experimental, Pre-Post Comparative Study. *JMIR Nurs.* **2025**, *8*, e71535.
31. Masson-Meyers, D.S.; Andrade, T.A.M.; Caetano, G.F.; et al. Experimental Models and Methods for Cutaneous Wound Healing Assessment. *Int. J. Exp. Pathol.* **2020**, *101*, 21–37.