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Hydrolysed casein-a multifunctional approach to combat wound healing challenges

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ABSTRACT

Wounds remain a significant global health concern, often described as a "silent epidemic," with conventional topical therapies limited by antimicrobial resistance, high costs, and poor accessibility. Hydrolysed casein, obtained through enzymatic breakdown of milk proteins, has emerged as a promising therapeutic alternative due to its antimicrobial, antioxidant, and anti-inflammatory properties. This review consolidates evidence published between 2014 and 2024 from PubMed, Embase, and Scopus, highlighting the role of hydrolysed casein in wound healing. Of 37 identified studies, 12 met inclusion criteria. Findings demonstrate that hydrolysed casein exhibits broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, viruses, fungi, and parasites. In addition, it modulates immune responses by suppressing pro-inflammatory cytokines and enhances granulation tissue formation, while its antioxidant activity protects tissues from oxidative stress. Various innovative delivery platforms—including hydrogels, nanofibers, micelles, and composite scaffolds—have been explored to improve stability, bioavailability, and clinical applicability. These systems offer controlled release, ease of administration, and cost-effectiveness. Collectively, hydrolysed casein represents a multifunctional, resistance-free, and affordable therapeutic candidate for wound healing, with significant translational potential for future clinical use.

Keywords: Hydrolysed Casein, Wound Healing, Milk Proteins, Bioactive Peptides, Antimicrobial Resistance, Antioxidants, Topical Administration, Hydrogels, Nanofibers

1. INTRODUCTION

Wounds have been a persistent challenge to humanity since the origin of our species. By definition, a wound represents a complete or partial loss of the structural and functional integrity of living tissues such as skin, mucosa, or internal organs, often caused by mechanical trauma, burns, or other insults to the epithelial barrier.[1,2]

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In recent years, chronic wounds have emerged as a major global health concern, sometimes referred to as a "silent epidemic." Estimates suggest that nearly 8 million individuals worldwide suffer from chronic wounds, contributing not only to significant morbidity but also to a substantial financial burden on healthcare systems.[3] Beyond physical discomfort, these wounds exert a profound influence on patients' psychosocial well-being and daily functioning.[4] In developed nations, between 1–2% of the population is expected to experience a chronic wound at some point in life. In the United States alone, approximately 8.5 million people are affected, with annual expenditures approaching 28 billion USD.[5] In the United Kingdom, chronic wound care consumes nearly 1.94 billion pounds annually, representing about 5.5% of the National Health Service budget.[6]

Epidemiological data also highlight the prevalence of both acute and chronic wounds at the community level. For instance, one study reported 4.5 chronic wounds per 1,000 individuals, whereas acute wounds were observed at 10.5 per 1,000.[7] Socioeconomic status further influences wound management outcomes, underscoring the need for cost-effective strategies that not only minimize morbidity but also reduce treatment-associated financial strain.[8]

Given these challenges, addressing wound healing effectively requires innovative interventions that improve healing outcomes while curbing the broader clinical and economic consequences.

2. METHODOLOGY

This narrative review was designed to consolidate and interpret the most recent evidence on wound-healing strategies, with a special emphasis on bioactive peptides derived from milk proteins such as casein. The objective was to summarize available data regarding the mechanisms of action, therapeutic potential, safety, and formulation strategies associated with these peptides, thereby generating a comprehensive reference for future clinical and research applications.

A systematic search of the literature was performed across PubMed, Embase, and Scopus, covering studies published in English between 2014 and 2024. The search strategy incorporated relevant Medical Subject Headings (MeSH) terms and keywords such as wound healing, hydrolysed casein, milk proteins, bioactive peptides, antioxidant, Antimicrobial Resistance, Topical Administration, Hydrogels, Nanofibers and recent advances. Articles were screened independently by two reviewers to ensure quality and consistency. Eligible studies were limited to those providing complete research findings, while non-randomized controlled trials, case reports, non-English articles, and commentaries were excluded.

Quality assessment of the included studies was undertaken using a pre-validated checklist to minimize bias. The synthesis of evidence was performed thematically, enabling the integration of findings into logical sub-sections addressing mechanisms, clinical relevance, and formulation approaches. As this work represents a narrative review, ethical approval was not required. Proper attribution was ensured through rigorous referencing, thereby acknowledging the contributions of original authors. A total of 37 articles were initially identified through database searches. After applying inclusion and exclusion criteria, 12 studies were considered eligible for final evaluation. These publications collectively explored the therapeutic applications of casein-derived bioactive peptides in wound healing, addressing their antimicrobial activity, immunomodulatory potential, antioxidant properties, and the development of novel formulations.

Mechanism of Action

Hydrolysed casein exerts its therapeutic potential through a combination of antimicrobial, antioxidant, and immunomodulatory pathways. Enzymatic hydrolysis of casein generates smaller peptide fragments that disrupt microbial membranes, inhibit adhesion, and interfere with replication.[9] These peptides also act as free radical scavengers, reducing oxidative stress at wound sites. Additionally, hydrolysed casein modulates immune responses by downregulating pro-inflammatory mediators such as TNF-α, IL-1β, and NF-κB, while enhancing lymphocyte proliferation and granulation tissue formation.[10] This multifaceted mechanism allows hydrolysed casein to address several overlapping phases of wound repair simultaneously, unlike many conventional single-target therapies.

Clinical Relevance

The multifunctional actions of hydrolysed casein translate into tangible clinical benefits for wound management. By reducing infection risk, controlling inflammation, and protecting tissues from oxidative injury, hydrolysed casein accelerates wound closure and improves tissue quality.[11] Preclinical studies have shown enhanced re-epithelialization and collagen deposition, while innovative formulations such as hydrogels, nanofibers, and micelles have improved stability and localized delivery. These properties position hydrolysed casein as a cost-effective, resistance-free, and adaptable candidate

for managing both acute and chronic wounds. Its compatibility with various delivery platforms further enhances its potential for clinical translation in diverse wound types.

Casein in Wound Healing

Beyond its antimicrobial activity, hydrolysed casein functions as a potent immune-modulator and antioxidant. Histological studies reveal improved granulation tissue formation and reduced expression of inflammatory cytokines such as TNF-α and IL-6.[7] Its phosphate-rich peptide fragments act as free radical scavengers, protecting cellular integrity during the reparative phase. Collectively, these findings highlight the dual role of hydrolysed casein in promoting tissue repair and countering inflammatory and oxidative damage.

Antibacterial Spectrum of Hydrolysed Casein Peptides

Enzymatic hydrolysis of casein also yields several peptides with broad-spectrum antibacterial activity. These peptides act against Gram-positive and Gram-negative bacteria, as well as fungi, viruses, and parasites. The most prominent examples are summarized in Figure 1.

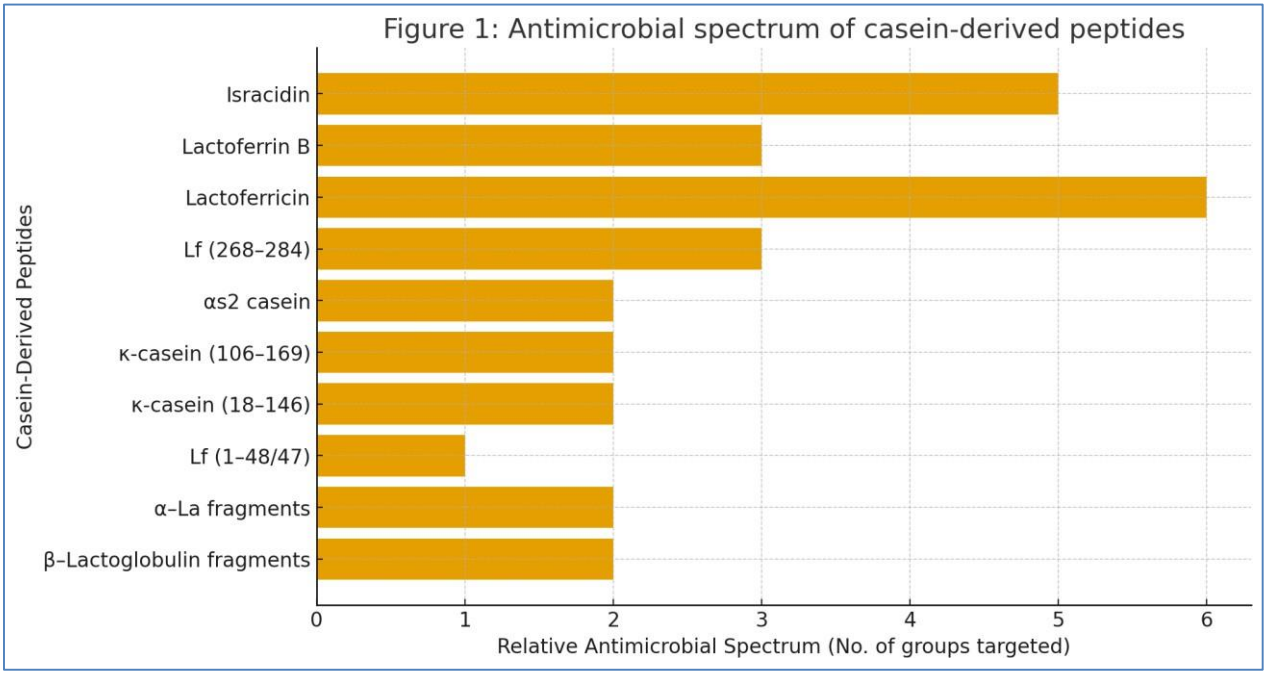

Figure 1. *Antimicrobial spectrum of casein-derived peptides.* The bar chart illustrates the relative breadth of microbial groups targeted by various casein-derived peptides. Lactoferricin and Isracidin display the widest antimicrobial range, including Gram-positive and Gram-negative bacteria, viruses, fungi, and parasites.

Available Formulations

A variety of innovative formulations have been developed to improve the stability, bioavailability, and clinical applicability of hydrolysed casein. These include hydrogels, nanofibers, micelles, and composite scaffolds, each offering unique advantages for wound healing. Hydrogels provide sustained release and moisture balance, nanofibers mimic the extracellular matrix and promote cell adhesion, while micelles and composites enhance drug loading and targeted delivery.[12] A summary of notable preparations is shown in Table 1.

The progressive evolution of these formulations over the past decade reflects increasing sophistication in design and functionality, as depicted in Figure 2. Early platforms, such as simple composite hydrogels, have now advanced to

multifunctional wound dressings with integrated antimicrobial and hemostatic properties. This trend demonstrates the adaptability of hydrolysed casein in diverse biomaterial constructs.

Furthermore, comparative analyses of different formulations reveal significant variations in wound closure rates. As illustrated in Figure 3, casein-cellulose scaffolds and fibers demonstrate faster healing times compared to certain composite hydrogels, highlighting the influence of material composition and structural design on therapeutic outcomes. Such findings underscore the importance of tailoring delivery systems to specific wound contexts for optimal results.

Table 1. Casein-based formulations explored for wound healing

Preparation	Key Findings
Antiseptic-loaded casein hydrogels	Effective wound dressings with sustained release of antiseptics
Casein fibers	Enhanced wound closure and tissue integration
Milk protein-based crosslinkable hydrogel	Ultrafast gelation bioadhesive for emergency wound treatment
Alginate-casein-bacterial cellulose hydrogel with Fe nanoparticles	Improved structural integrity and antibacterial action
Casein + oxidized hyaluronic acid hydrogels	Biocompatible composite for controlled drug release
Caseinate/gelatin nanocomposite hydrogel	In vivo antibacterial and wound healing properties
Casein micelle organo-hydrogel	Potential scaffold for wound dressings
Casein-cellulose nanofibril composite	Hemostatic scaffold promoting faster healing
Chitosan-casein nanofibrous complex	Hybrid nanofiber with rapid hemostatic activity
Multifunctional casein wound dressing	Monitors proteolytic activity in chronic wounds

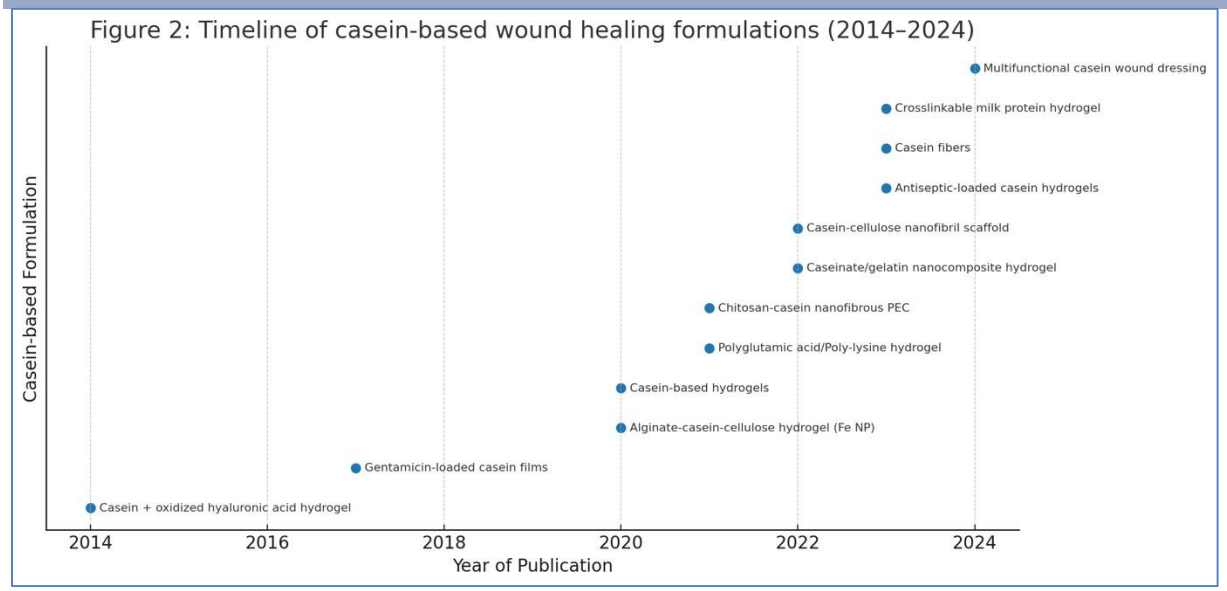

Figure 2. *Timeline of casein-based wound healing formulations (2014–2024).* This timeline highlights the progressive development of diverse casein formulations, from early composite hydrogels in 2014 to multifunctional wound dressings in 2024. The trend reflects increasing sophistication and clinical applicability.

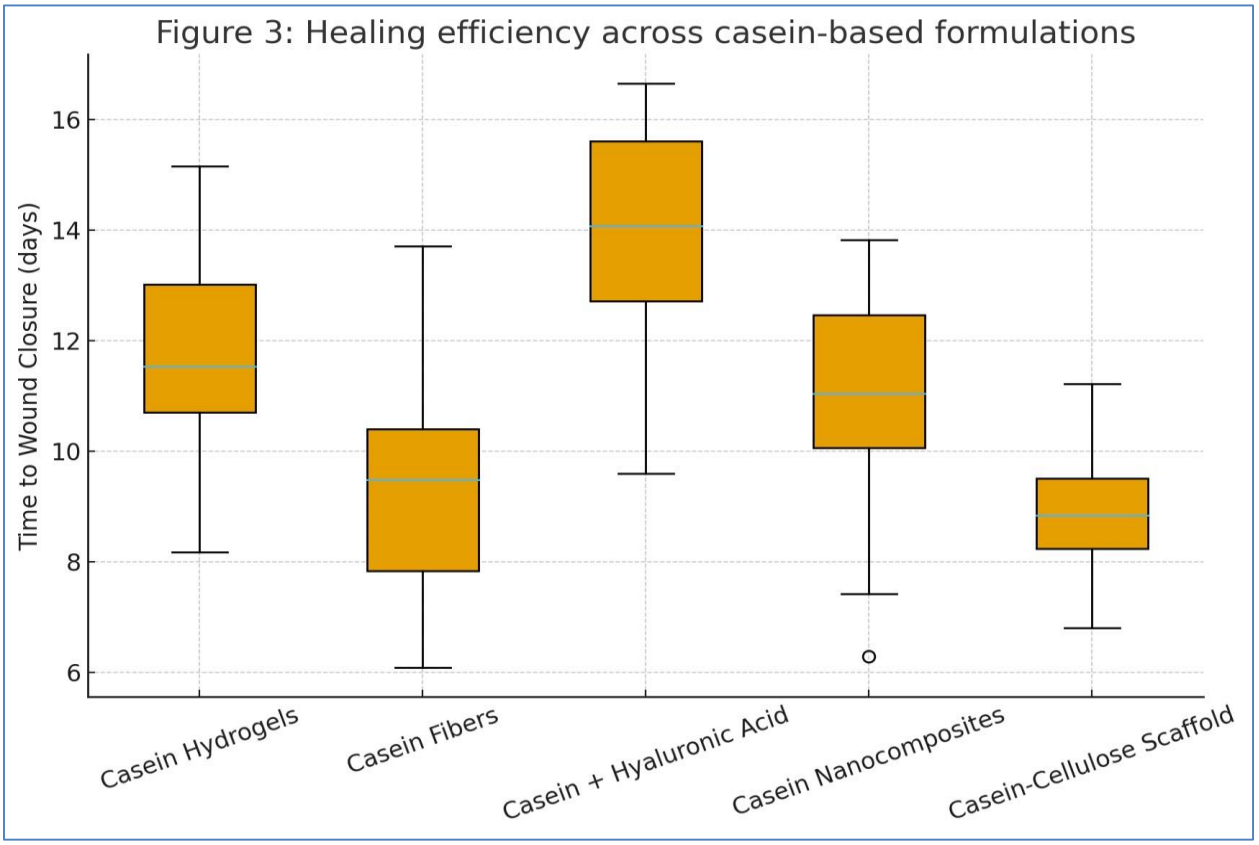

Figure 3. *Healing efficiency across casein-based formulations.* The box plot compares time to wound closure among different casein-derived preparations. Casein-cellulose scaffolds and fibers show relatively faster healing times, while composite hydrogels incorporating hyaluronic acid exhibit longer recovery durations.

3. DISCUSSION

The findings of this review emphasize the multifaceted role of casein-derived peptides in the wound healing process. Wound repair is inherently complex, involving overlapping stages of inflammation, proliferation, and remodeling.[13,14] Any disturbance in these steps, whether due to infection, systemic illness, or lifestyle-related factors, can significantly delay healing.[15,16] Hence, novel therapeutic strategies that address these multiple dimensions simultaneously are of high clinical importance.

A recurring challenge in wound care is microbial colonization, which not only delays epithelialization and granulation but also predisposes to chronic infections.[17] Conventional topical antimicrobials, though widely used, are associated with increasing resistance among pathogens such as *Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa,*and *Acinetobacter baumannii*.[18,19] This situation has driven the search for agents that remain effective without fostering resistance. In this regard, bioactive peptides offer a promising alternative.

Casein-derived peptides demonstrate broad antimicrobial activity through mechanisms such as membrane disruption and inhibition of microbial adhesion, making them effective against both Gram-positive and Gram-negative bacteria.[20,21] Their ability to bypass classical resistance pathways underscores their clinical value. Furthermore, their immunomodulatory role, including the enhancement of lymphocyte proliferation and suppression of pro-inflammatory cytokines like TNF-α, IL-1β, and NF-κB, provides additional benefit by creating a favorable environment for tissue repair.[22,23]

Another noteworthy property of casein peptides is their antioxidant capacity, which arises from phosphate-rich subunits that act as free radical scavengers.[24] By mitigating oxidative stress, casein peptides protect cellular integrity during the reparative phase, thereby accelerating healing. Additionally, research into tripeptides such as Val-Pro-Pro and Ile-Pro-Pro highlights their ability to attenuate cytokine-driven inflammation and modulate metabolic processes.[25,26] These combined antimicrobial, anti-inflammatory, and antioxidant actions distinguish casein peptides from many conventional therapeutic options.

The exploration of novel formulations, including hydrogels, nanofibers, micelles, and composites, further enhances the applicability of casein in clinical settings.[27-31] Such systems not only improve peptide stability and bioavailability but also enable controlled release, localized delivery, and integration with other therapeutic agents. Notably, composite hydrogels and casein-cellulose scaffolds have shown encouraging outcomes in preclinical studies, reinforcing the versatility of casein-based biomaterials.

Despite these promising findings, several gaps remain. The majority of available studies are preclinical or based on small experimental models, limiting direct translation into clinical practice.[32-35] Additionally, heterogeneity in study designs and endpoints complicates data comparison. A concerted effort toward large-scale, well-controlled clinical trials is therefore essential to establish standardized dosing, safety profiles, and long-term outcomes of casein-derived wound therapies.

Taken together, casein peptides hold substantial potential as a cost-effective, resistance-free, and multifunctional therapeutic approach for wound management. Their ability to target infection, inflammation, and oxidative damage simultaneously positions them as an attractive adjunct or alternative to conventional treatments.

4. STUDY LIMITATIONS

This review has certain limitations that should be acknowledged. First, the discussion was primarily centered on casein-derived peptides, without exploring in depth the broader spectrum of bioactive peptides that may also contribute to wound repair. As a result, the findings may not fully represent the wider field of peptide-based wound therapeutics. Second, variations in study designs, animal models, and population demographics across the included studies introduce heterogeneity, which may influence the comparability and generalizability of results. Third, reliance on published literature may carry an inherent publication bias, as studies with positive findings are more likely to be reported than those with negative or inconclusive outcomes. Finally, this review did not extensively evaluate long-term clinical safety or standardized administration methods, which remain important considerations for translation into practice.

5. SUMMARY AND CONCLUSION

Wound healing remains a significant clinical challenge, often complicated by microbial colonization, delayed tissue repair, and the growing issue of antimicrobial resistance. Traditional topical agents and advanced therapies such as growth factors or gene-based approaches, while effective in some contexts, are limited by high cost, reduced accessibility, and the risk of resistance.

Casein-derived peptides emerge as a promising alternative owing to their broad-spectrum antimicrobial, antioxidant, and anti-inflammatory activities. Their unique ability to act across multiple levels of the healing cascade, combined with their natural origin, cost-effectiveness, and compatibility with diverse formulations, highlights their translational potential in wound care. The availability of innovative delivery systems—such as hydrogels, nanofibers, micelles, and scaffolds—further enhances the stability and applicability of casein peptides, making them versatile candidates for clinical use. Importantly, their efficacy is not undermined by conventional resistance mechanisms, which positions them as sustainable therapeutic options in the face of global antimicrobial resistance. Future efforts should prioritize well-structured, large-scale clinical trials to validate safety, optimize dosing strategies, and establish standardized protocols. With continued research, casein-derived peptides could transition from experimental promise to a mainstream therapeutic tool, offering affordable and effective wound healing solutions worldwide.

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