UDC: 616-001.45:616-085-089
DOI: https://doi.org/10.32345/USMYJ.2(1623).2026.28-35

Biochemical factors of wound healing: prospects and limitations of application in clinical practice

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Abstract. *Introduction.* The full-scale war in Ukraine has led to a significant number of wounded among both military personnel and civilians. Combat injuries often become chronic due to limited access to medical care and a high risk of wound infection. In addition, chronic wounds, particularly diabetic foot ulcers and venous ulcers, continue to represent a major healthcare problem because of their high prevalence. An imbalance of biochemical factors that regulate the process of wound healing at the stages of inflammation, angiogenesis, proliferation, and remodelling can contribute to the chronicity of wounds.
Aim. In this review, we analyse the role of biochemical regulators at different stages of tissue repair and consider the possibilities of integrating these data into clinical practice.
Materials and Methods. Approximately 50 literature sources were analysed. Articles from PubMed, Mendeley, and Europe PMC databases, as well as specialised Ukrainian journals, were used. We selected the most characteristic biochemical factors for each stage of tissue repair, as well as those with the greatest therapeutic potential.
Results. The following biochemical factors were examined: haemostatic components (thrombin and fibrin), inflammatory mediators (IL-10, MMPs/TIMPs), angiogenesis and proliferation regulators (VEGF, PDGF), gasotransmitters (H_2S), and extracellular matrix components (hyaluronic acid). Each group demonstrated therapeutic potential in experimental and, to a significantly lesser extent, in clinical settings.
Conclusions. However, the clinical application of these biomolecules is limited by molecular instability, dose-dependent risks, high cost, and a lack of standardisation. Therefore, optimisation of delivery systems and the conduct of high-quality clinical studies are required.

Keywords: angiogenesis, biomarkers, extracellular matrix, inflammation, intercellular signaling peptides and proteins, interleukins, regeneration, wounds and injuries.

Introduction

The process of tissue repair consists of four phases: haemostasis, inflammation, proliferation, and remodeling [1]. Disruption of one or more phases of the wound healing process can lead to chronic wound formation - including diabetic foot and venous leg ulcers, which represent a significant public health problem and affect millions of patients worldwide [2]. Armed conflicts, and in particular the war in Ukraine, exacerbate the problem of chronic wounds due to reduced access to medical care, which increases the frequency of infections, complications, and amputations [3].

Aim

The aim of this study is to summarise current data on the role of biomolecules at different stages of tissue repair and to analyse the prospects and limitations of their clinical application, especially in conditions of increased medical and social burden caused by war.

Materials and Methods

A literature search was conducted in the PubMed, Mendeley and Europe PMC databases and specialised Ukrainian journals using the keywords: angiogenesis, biomarkers, extracellular matrix, inflammation, intercellular signaling peptides and proteins, interleukins, regeneration, wounds and injuries.

The literature search included publications from 2015 to 2025, as well as several earlier studies considered essential for understanding the biological mechanisms of wound healing. Only primary research articles were selected for this review, while conference abstracts were excluded. Articles not directly related to the biochemical regulation of wound healing were excluded.

In total, 50 scientific publications were included in the final review.

Table 1: Biochemical factors in wound healing: applications, effects and limitations

Biochemical factors	Forms and stages of application	Biological effects on wound healing	Limitations of use
Thrombin and fibrin	**Clinical application** (fibrin sealants, fluid sealing [4-6]) **Experimental model** (composite sponges, 3D bioprinting skin [7-8], fibrin-based materials - hydrogels [9])	Haemostatic and regenerative properties [4,5,8,10-12]	Short half-life [9], risk of thrombosis, hypersensitivity reactions [5,13-14], immunogenicity [4,13]
Interleukin-10 (IL-10)	**Clinical trials** (rhIL-10 in volunteers [15]) **Experimental model** (recombinant IL-10 [16-18])	Anti-inflammatory and anti-fibrotic activity [19]	Short half-life; immunosuppresson risk [16-17]
Hydrogen sulfide (H_2S)	**Experimental model and prospective technology** (donors of H_2S [20-22])	Antioxidant and anti-inflammatory properties [20-23]	Instability, dose-dependent effects [20-22]
VEGF and PDGF	**Clinical application** (Becaplermin, PRP [9,24]) **Experimental model** (Salidroside [25-26]) **Promising technology** (delivery systems [27-28])	Stimulation of angiogenesis and cell proliferation [9-10,29-31]	Chronic inflammation [32], scarring and malignancy [9], low bioavailability in vivo [9,14,33]
Hyaluronic acid (HA)	**Clinical application** (HA-wound dressings and gauze pads [34]) **Preclinical/experimental model** (composite scaffolds, modified HA formulations [34-35])	Regulation of cell proliferation [34]	Low mechanical strength; lack of haemostatic and antimicrobial properties [34]

Review and discussion

Haemostasic phase

Thrombin and fibrin are key components of the coagulation cascade [4,8]. In addition to their haemostatic function, they promote cell proliferation and support tissue repair [9–10,24,36].

Thrombin and fibrin combine high biocompatibility with both haemostatic and regenerative properties, which leads to their wide use in local haemostatic materials [4]. Rapid cessation of bleeding in combat conditions is essential for maintaining life and ensuring effective subsequent wound healing.

Fibrin sealants, such as Tisseel, are used in clinical practice to achieve haemostasis. They combine haemostatic, sealing, and adhesive properties, which reduces the need for additional haemostatic agents [4–5]. In skin burn models, which are often encountered in mine-explosive injuries, fibrin sealants have promoted skin grafting and improved wound closure [5]. Fluid haemostatic sealing materials composed of thrombin and fibrinogen are suitable for deep wound bleeding due to their high fluidity, particularly in cases of internal bleeding, which often occurs in combat injuries. These materials mimic the physiological conversion of fibrinogen to fibrin. A significant drawback of their application is excessive fibrosis [6].

In preclinical mouse models, local application of thrombin-containing matrices reduces blood loss and promotes wound healing; however, systemic entry of thrombin may increase the risk of thrombosis [8,10–13]. The application of a thrombin-loaded silk fibroin–gelatin composite haemostatic sponge (SFG@TB) demonstrated a higher wound-healing rate compared with the gelatin (GE) and silk fibroin–gelatin (SFG) groups. Thrombin in SFG@TB initiates haemostasis, the first phase of wound healing [8].

Fibrin-based materials, including sheets, bandages, and hydrogels, provide rapid haemostasis in animal models of severe trauma and ballistic injuries, demonstrating their effectiveness in combat-related injuries [9]. In diabetes and obesity models, fibrin hydrogels enriched with growth factors (VEGF, PDGF-BB) protect biomolecules from degradation and ensure their controlled release, thereby enhancing wound healing [37]. Fibrin also exhibits biomimetic properties. For instance, 3D-bioprinted skin using fibrinogen-based bioink promotes cell proliferation in experimental models [7].

Limitations of use

Thrombin is characterized by a short half-life (about 15 seconds) [9], which necessitates the use of delivery systems. The immunogenicity of animal thrombin and the risk of viral transmission of human plasma-derived products are additional limitations [4,13]. However, the use of recombinant forms of thrombin is restricted by high cost [9]. Clinical studies have shown that the use of fibrin sealants in knee replacement surgery provides no significant clinical benefit. Moreover, their application is limited by high costs, hypersensitivity reactions, and local inflammatory responses [5].

A promising direction for future research is the development of combined haemostatic agents that

integrate analgesic and antimicrobial properties. Such multifunctional formulations could not only enhance haemorrhage control but also reduce pain and lower the risk of wound infection, which would be especially beneficial on the battlefield, where access to advanced medical care is often delayed [9].

Inflammation phase

The inflammatory phase is critical for the subsequent course of wound healing, as it determines progression to the proliferative phase or the development of chronicity.

Chronic wounds are characterized by a dysregulated balance between proteases and their inhibitors, as well as between pro- and anti-inflammatory cytokines [38]. Increased activity of MMP-2, MMP-8 and MMP-9 is associated with persistent inflammation and poor healing outcomes [38-40]. Levels of IL-10 are reduced, whereas expression of IL-1α, IL-1β, IL-6, TNF-α, and IL-8 is elevated in the blood, wound fluid, and biopsies of chronic wounds - diabetic and venous foot ulcers [38-41]. During the healing process, their levels decrease, while TGF-β1 increases [41]. Increased bacterial burden may further sustain inflammation by stimulating excessive production of pro-inflammatory mediators [39], a mechanism that may be particularly relevant in combat wounds.

The use of IL-1β and TNF-α as isolated biomarkers is limited due to their correlation with severe inflammation, bacterial contamination, and slow wound healing. The most potentially significant predictors of healing are granulocyte-macrophage colony-stimulating factor (GM-CSF) and metalloproteinase-13 (MMP-13) [38].

As mentioned above, chronic wounds are characterized by reduced **IL-10** expression and increased levels of pro-inflammatory cytokines and matrix proteases. The abnormal inflammation results in pathological scarring [42]. Therefore, IL-10 participates in both the inflammatory and remodeling phases of wound healing. Through its anti-inflammatory activity, IL-10 limits excessive immune responses, whereas its anti-fibrotic properties help regulate extracellular matrix deposition and reduce pathological scarring [19,44]. These effects make IL-10 a promising therapeutic agent for improving tissue repair and promoting more favorable wound remodeling.

To better understand the role of IL-10 in tissue repair, findings from several studies performed in murine models are discussed below. A 2023 study demonstrated excessive inflammation and fibrosis of the wound bed when comparing IL-10$^{-/-}$ mice to wild-type (WT) mice, but wound closure was no different between the two groups [19]. However, increased expression of IL-10 was shown to promote revascularization and re-epithelialization in control and diabetic models, thereby promoting accelerated wound healing [14]. IL-10 administration before transplantation also improved tissue healing capabilities [18]. These findings suggest that IL-10 deficiency does not necessarily impair the rate of wound closure but is associated with enhanced inflammation and fibrosis, which may lead to poor quality of tissue repair.

In a recent clinical trial, recombinant human IL-10 (rhIL-10) was administered to healthy volunteers, resulting in improved macroscopic scar appearance [15]. The anti-fibrotic effects of IL-10 indicate that this cytokine may represent a promising strategy for both scar prevention and the reduction of pathological scar formation.

Limitations of use

The application of IL-10 is limited due to its short half-life in vivo [16-17], necessitating the development of controlled-release delivery systems for IL-10.

Systemic administration of IL-10 also leads to flu-like symptoms. High levels of IL-10 can lead to a risk of infection [16].

Therefore, the clinical application of IL-10 requires careful optimization to achieve anti-inflammatory effects while minimizing the risk of immunosuppression.

Hydrogen sulfide (H_2S) is a gasotransmitter whose role in wound healing is most pronounced during the inflammatory phase, where it regulates inflammatory responses and oxidative stress. These properties may provide further application of H_2S as a potential therapeutic agent for various traumatic conditions, including combat injuries [44].

In the setting of combat-related trauma, traumatic CNS injuries are among the most severe consequences characterized by secondary pathological processes, including neuroinflammation and oxidative stress [21,23,45]. Preclinical studies have demonstrated that H_2S can attenuate secondary injury through anti-inflammatory and antioxidant mechanisms, while also promoting neuroregeneration. However, all available data derive from animal models, and further studies are required to establish safety and clinical efficacy. In diabetic patients, H_2S levels are decreased, and impaired healing is associated with persistent inflammation and excessive superoxide production [21,23] - features shared with traumatic and combat-related wounds.

To date, no clinical studies have evaluated H_2S-based therapies in wound healing, and current evidence is limited to preclinical investigations. In preclinical models, $O2\bullet^{-}$-activated H_2S donors such

as HSD-SO-B demonstrated selective activation in oxidative environments and accelerated wound closure [20]. Similarly, NaHS promoted healing and angiogenesis via VEGF upregulation in diabetic mice [21-23].

Limitations of use

Despite this therapeutic potential, clinical translation remains limited by H_2S volatility, instability, and dose-dependent biological effects [20-22]. NaHS, H_2S, and Lawesson's reagent-type compounds exhibit rapid and uncontrolled H_2S release and potential cytotoxicity [20-21]. To overcome these limitations, donors with controlled release are being developed. These include nanomaterials, hydrogels and smart delivery systems capable of responding to injury-specific stimuli such as pH changes or oxidative stress, which provide more sustained H_2S release [21], but require further clinical validation before routine use [44].

Proliferative phase

Angiogenesis is a key process in the proliferative phase of wound healing. **Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)** are major regulators of this phase [9,32,46-47]. VEGF primarily stimulates the formation of new blood vessels, while PDGF-BB promotes vessel maturation and stabilization through the activation of pericytes [30-31,46]. Thus, VEGF and PDGF exert complementary effects during tissue repair.

Evidence supporting the clinical efficacy of both PDGF and VEGF can be found in platelet-rich plasma (PRP). The the rapeutic effect of PRP is associated with the combined action of growth factors which stimulate angiogenesis, granulation tissue formation, and tissue repair. PRP is used in clinical practice for treatment of chronic wounds. However, variations in PRP preparation may affect growth factor concentrations and clinical outcomes [24].

In clinical practice, PDGF-BB is applied as the topical formulation Becaplermin for the treatment of chronic wounds. By delivering this growth factor directly to the wound site, the formulation stimulates neovascularisation and promotes granulation tissue formation [9,25]. In addition to its role in tissue repair, PDGF-AA has been proposed as a biomarker of wound healing, as elevated levels in wound exudate and plasma have been associated with successful healing of chronic venous ulcers [38,40].

Several experimental studies have shown that the therapeutic potential of PDGF can be realized not only through exogenous administration but also by inducing its endogenous expression, which reduces the risks associated with protein instability. For example, salidroside promotes neoangiogenesis by increasing VEGF-A and PDGF-BB secretion, thereby improving limb blood flow in diabetic mice [25-26].

While PDGF-BB has been translated into clinical practice through the FDA-approved formulation Becaplermin, VEGF-based therapies remain at the preclinical stage. In experimental study on diabetic mice, treatment with the fusion protein F8-VEGF-C promoted wound healing and lymphangiogenesis in diabetic mice, indicating the therapeutic potential of lymphatic system activation in chronic wounds [48]. Experimental studies have shown that inhibition of VEGF signaling impairs wound healing in animal models. Clinical studies demonstrate reduced VEGF levels in chronic diabetic ulcers compared with acute wounds, whereas normal VEGF expression correlates with improved healing outcomes [38,47,49].

Limitations of use

The effectiveness of growth factor-based therapy is limited by the low stability and short half-life of growth factors, together with reduced bioavailability due to high proteolytic activity in the wound environment. This necessitates the use of high doses, increasing the risk of adverse effects [9,14,33].

Although Becaplermin is successfully used in practice, its efficacy is reduced in infected or ischaemic wounds [9]. This limitation is particularly relevant to chronic battlefield-associated injuries, which are frequently contaminated and characterised by impaired tissue perfusion. Furthermore, prolonged or excessive use of Becaplermin has been associated with a potential increase in the risk of malignancy [9].

The therapeutic application of VEGF requires careful regulation, as both insufficient and excessive expression may impair wound healing. Excessive VEGF activity can increase vascular permeability and sustain chronic inflammation [32]. Several studies have found that VEGF concentrations in wound fluid are significantly higher in poorly healing venous leg ulcers than in those that heal. Elevated VEGF levels correlate with scarring, while VEGF inhibition may limit scar formation [40-41,47].

To provide sustained release of growth factors, delivery systems are being developed. Microspheres and liposomes are being incorporated into hydrogels [24]. A recent review highlighted that "smart" hydrogels are able to respond to changes in the wound microenvironment by modulating the release rate of growth factors [27-28].

Hyaluronic acid (HA) is a key component of the extracellular matrix that regulates cell proliferation, differentiation, and migration, contributing primarily to the proliferative phases of wound healing [34]. Due to its biocompatibility and moisture-retaining capacity,

hyaluronic acid (HA) is used as a therapeutic agent for chronic ulcers and infected traumatic wounds.

Clinical evidence supports the use of HA-based dressings in chronic wounds. HA-impregnated gauze pads reduced venous ulcer area compared with control treatments [34]. Furthermore, HA-based formulations combined with antimicrobial agents, including silver, achieved up to a 99% reduction in wound volume in patients with vascular and pressure ulcers, which is particularly effective for infected or contaminated wounds [35,50].

In experimental models, composite HA/SF/SA (hyaluronic acid/silk fibroin/alginate) scaffolds demonstrated wound size reduction. In addition, they exhibited enhanced tensile strength, biocompatibility, biodegradability, and moisture management [34-35]. Chemical modification of HA, including thiolation and esterification-stimulated angiogenesis and reduced ulcer area in preclinical studies of venous and diabetic wound models [34].

Limitations of use

HA hydrogels exhibit insufficient mechanical strength, while the incorporation of synthetic polymers may impair exudate drainage. Hydrocolloid dressings are unsuitable for bleeding wounds and have low stability and high cost [34]. In combat wound contexts specifically, unmodified HA lacks adequate haemostatic and antimicrobial properties.

Expanding the clinical applicability of hyaluronic acid-based formulations requires the integration of HA with protein, polysaccharide, and antimicrobial components, the development of nanocomposite hydrogels, and the chemical modification of HA to increase adhesive and haemostatic properties [34]. Supplementation with antimicrobial compounds remains essential to prevent infection - a priority in the management of combat-related wounds [34].

Remodelling phase

Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) play a central role in the remodeling phase by regulating extracellular matrix turnover and granulation tissue formation [38-39]. Balanced MMPs/TIMPs activity is essential for proper tissue maturation, whereas dysregulation of this system contributes to chronic wounds and pathological scar formation. A high MMP-1/TIMP-1 ratio has been associated with effective tissue regeneration [38-40].

As discussed above, several biomolecules involved in earlier phases of wound healing continue to influence tissue remodeling. IL-10 contributes to the remodeling phase through its anti-fibrotic activity [15,18-19,42-43]. VEGF signaling requires tight regulation during remodeling, as excessive VEGF expression has been associated with hypertrophic scarring and aberrant wound remodeling [40-41,47]. Hyaluronic acid, previously described as a key extracellular matrix component during the proliferative phase, also participates in tissue maturation and extracellular matrix organization [34].

Conclusions

This literature review demonstrates that the examined biochemical factors have potential for application both as isolated biomolecules and as components of delivery systems designed to ensure controlled release in the wound microenvironment. However, the clinical use of these compounds is restricted by molecular instability, dose-dependent biological effects, high material costs, and a lack of standardised protocols for clinical studies. To expand their clinical application, further development of delivery systems is required. Standardisation of measurement methods and the conduct of high-quality clinical studies are also essential.

Article Declarations / Пристатейні розділи

Raw Data and Materials. The raw data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Limitations. This review has several methodological limitations that should be considered when interpreting the findings. First, no formal assessment of risk of bias was performed for the included studies, and no meta-analysis was conducted; therefore, the synthesised findings represent a narrative rather than a systematic review. Second, a significant part of the conclusions are based on preclinical or experimental data derived from animal models, which may not fully correspond to human clinical outcomes. Third, the search was limited to publications in English and Ukrainian, which could lead to the exclusion of relevant studies published in other languages.

Funding. This review is part of a funded research program and was supported by the Ministry of Health of Ukraine (Order No. 98 of 27 January 2026, "Screening of wound-healing and anti-inflammatory effects of complex drugs based on natural and synthetic disulphide compounds and biosurfactants").

Ethics Approval Statement. Was not required for this study because it is a literature review based on previously published data.

Conflict of Interest. The authors declare no conflicts of interest related to the publication of this article. All authors have read the manuscript and gave their consent for its publication.

AI Statement. The authors used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. **The** authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

Author Contributions (CRediT)

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Біохімічні чинники загоєння ран: перспективи та обмеження застосування в клінічній практиці

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Анотація. *Вступ.* Повномасштабна війна в Україні призвела до значної кількості поранених як серед військовослужбовців, так і серед цивільного населення. Бойові поранення часто переходять у хронічну форму через обмежений доступ до медичної допомоги та високий ризик інфікування ран. Крім того, хронічні рани, зокрема діабетичні виразки стопи та венозні виразки, залишаються серйозною проблемою для системи охорони здоров'я через високу поширеність. Дисбаланс біохімічних факторів, що регулюють процес загоєння ран на стадіях запалення, ангіогенезу, проліферації тканин та ремоделювання, може спровокувати хронізацію уражень.

Мета. У цьому огляді ми проаналізували роль біохімічних регуляторів на різних стадіях відновлення тканин та розглянули можливості впровадження цих даних у клінічну практику.

Матеріали та методи. Було проаналізовано близько 50 літературних джерел. Використовувалися статті з баз даних PubMed, Mendeley та Europe PMC, а також спеціалізованих українських журналів. Ми відібрали найбільш характерні біохімічні фактори для кожного етапу відновлення тканин, а також ті, що мають найбільший терапевтичний потенціал.

Результати. Були досліджені такі біохімічні фактори: гемостатичні компоненти (тромбін та фібрин), медіатори запалення (IL-10, MMPs/TIMPs), регулятори ангіогенезу та проліферації (VEGF, PDGF), газотрансмітери (H_2S) та компоненти позаклітинного матриксу (гіалуронова кислота). Кожна група продемонструвала терапевтичний потенціал в експериментальних умовах та значно менший — у клінічних.

Висновки. Однак клінічне застосування цих біомолекул обмежується нестабільністю молекул, дозозалежними ризиками, високою вартістю та відсутністю стандартизації. Тому необхідна оптимізація систем доставки та проведення високоякісних клінічних досліджень.

Ключові слова: ангіогенез, біомаркери, запалення, інтерлейкіни, міжклітинні сигнальні пептиди та білки, позаклітинний матрикс, поранення і травми, регенерація.

Received: February 14, 2026
Accepted: April 09, 2026
Published online: June 30, 2026