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Therapeutic Potential of Topical Metformin in Diabetic Wound Healing: Preclinical Mechanistic Insights

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ABSTRACT

Diabetic wounds remain a major complication of diabetes mellitus due to persistent inflammation, oxidative stress, and impaired tissue regeneration, resulting in delayed healing and increased risks of infection and amputation. This review aimed to synthesize current preclinical evidence regarding the therapeutic potential of topical metformin by comparing different delivery systems, integrating the underlying molecular mechanisms, and discussing their translational potential. Across diverse experimental models, topical metformin consistently accelerated wound healing through activation of AMP-activated protein kinase (AMPK), suppression of NF-κB-mediated inflammation, attenuation of oxidative stress, promotion of macrophage polarization toward the M2 phenotype, enhancement of angiogenesis, and stimulation of extracellular matrix remodeling. Comparative analysis indicated that advanced delivery systems, including hydrogels, nanoparticles, microneedles, and exosome-assisted platforms, generally improved local drug retention and therapeutic efficacy compared with conventional topical formulations. However, the intrinsic biological activity of biomaterial carriers should also be considered when interpreting therapeutic outcomes. Overall, current preclinical evidence supports topical metformin as a promising immunometabolic therapeutic strategy for diabetic wound healing. Nevertheless, standardized formulations, pharmacokinetic evaluation, safety assessment, and well-designed clinical trials remain essential before routine clinical application can be recommended.

INTRODUCTION

Diabetes mellitus is a global health problem, with an estimated 537 million adults affected worldwide as of 2021, which is expected to increase up to 783 million by 2045 [1]. Diabetic foot ulcers (DFUs) are one of the most critical complications, occurring in approximately 19–34% of patients throughout their lifetime and are a leading cause of hospitalization and non-traumatic lower limb amputations [2,3]. Chronic diabetic wounds have been a global challenge with an escalating socioeconomical burden related to long-term wound care, infection control, surgery and rehabilitation outcomes [1,3]. Although multidisciplinary wound healing protocols have improved, results are still suboptimal, suggesting that existing models do not adequately target core biological derangements behind chronic diabetic wounds [4].

Chronic inflammation has emerged as a significant factor impeding the healing of diabetic wounds. Chronic hyperglycemia causes mitochondrial malfunction and too many reactive oxygen species (ROS) to be generated. This causes oxidative stress and activates nuclear factor-κB (NF-κB), which is a key transcription factor that governs the expression of inflammatory genes. Chronic NF-κB activation leads to elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF–α), interleukin-1β (IL1β) and interleukin-6 (IL6) which sustain the persistent inflammation status [5–7]. In addition, macrophage polarization is dysregulated in diabetic wounds. Under normal conditions, macrophages transition from a pro-inflammatory M1 phenotype to a reparative M2 phenotype during wound healing. However, this transition is impaired in diabetic conditions, resulting in prolonged inflammation and delayed tissue repair [7,8]. Furthermore, chronic inflammation disrupts angiogenesis by impairing vascular endothelial growth factor (VEGF) signaling and endothelial cell function, thereby hindering neovascularization and granulation tissue formation [9].

Metformin, widely established as a first-line antihyperglycemic agent, has attracted growing attention for its pleiotropic actions beyond glucose control. At the cellular level, metformin activates AMP-activated protein kinase (AMPK), a key metabolic sensor that exerts anti-inflammatory and antioxidative effects [10]. AMPK activation suppresses NF-κB signaling, reduces pro-inflammatory cytokine production, improves mitochondrial function, and attenuates ROS accumulation, mechanisms directly relevant to the pathological inflammatory milieu of diabetic wounds [10,11]. Emerging experimental data further suggest that metformin can influence macrophage polarization, enhance endothelial function, and promote angiogenic responses under metabolic stress conditions [5,11].

In this way, topical administration of metformin offers distinct advantages since it gives high local concentrations at the wound site while limiting systemic exposure. Recent preclinical studies have demonstrated the therapeutic potential of topical metformin for diabetic wound healing through multiple biological mechanisms and a variety of topical formulations [12–14]. However, the available evidence has been generated using different experimental models, formulation strategies, and outcome measures, making it challenging to obtain an integrated understanding of the current findings. In addition, recent studies have increasingly explored advanced delivery systems, highlighting the need for a comparative evaluation of these approaches within the context of preclinical evidence. Therefore, this review synthesizes the current preclinical evidence on the therapeutic potential of topical metformin in diabetic wound healing by integrating the reported molecular mechanisms, comparing the characteristics of different topical delivery systems, and discussing current translational considerations for future clinical development. In addition, this review identifies methodological limitations and evidence gaps that may help guide future preclinical and clinical studies.

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METHOD

Literature Search

This review was conducted using a structured literature review approach to identify relevant preclinical studies investigating the therapeutic potential of topical metformin in diabetic wound healing. The search was conducted from 10–15 January 2026, using three electronic databases: PubMed, Scopus, and ScienceDirect. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords using Boolean operators.

The primary search terms included "topical metformin", "metformin", "diabetic wound", "diabetic wound healing", "inflammation", "hydrogel", "nanoparticle", "microneedle", "drug delivery", "AMPK", and "NF-κB". An example of the search strategy was: ("topical metformin" OR "metformin") AND ("diabetic wound" OR "diabetic wound healing") AND ("inflammation" OR "AMPK" OR "NF-κB"). Only articles published in English between 2016 to 2026 were considered.

Study Selection

Relevant records were identified and screened according to predefined eligibility criteria to provide a structured overview of the available preclinical evidence. After removing duplicate records, titles and abstracts were screened for relevance. Potentially eligible articles then underwent full-text assessment before being included in the final review.

Studies were included if they: were original preclinical studies; investigated topical metformin or metformin-containing topical formulations; used diabetic wound animal models; evaluated wound healing outcomes and/or underlying molecular mechanisms; and were published in English.

Studies were excluded if they: investigated oral or systemic metformin administration only; were review articles, conference abstracts, editorials, letters, or case reports; did not evaluate diabetic wound healing; or lacked sufficient experimental information.

The flow diagram of the study selection process is presented in Figure 1.

Data Extraction and Synthesis

For each eligible study, the following information was extracted: author and publication year; experimental animal model; topical metformin formulation; metformin concentration or dose; delivery platform; molecular mechanisms investigated; and principal wound healing outcomes.

The extracted information was synthesized descriptively to compare the reported molecular mechanisms, topical delivery systems, and therapeutic outcomes across the included preclinical studies. Because of the heterogeneity in experimental models, formulations, treatment protocols, and outcome measures, no quantitative synthesis was performed.

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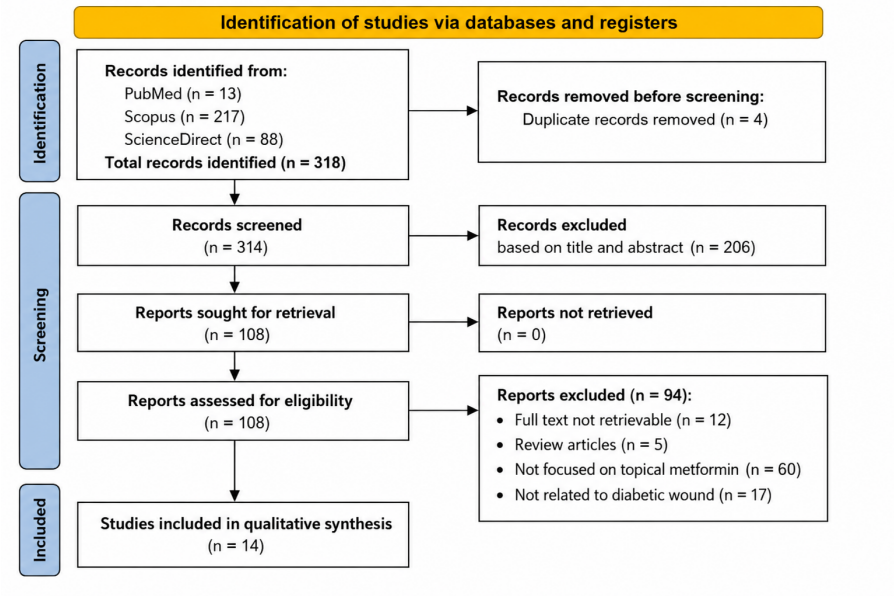

Figure 1. Article Selection Flowchart

RESULT AND DISCUSSION

A total of 14 eligible studies were included in the final synthesis after screening and selection. The studies included in the synthesis are shown in Table 1. Experimental animal models are essential for understanding the therapeutic effects of topical metformin on diabetic wound healing. Indeed, to recapitulate the metabolic and inflammatory alterations observed in chronic diabetic wounds, most studies have used streptozotocin (STZ)-induced diabetic rodents. These experimental models allow detailed investigation of the molecular mechanisms underlying impaired healing as well as evaluation of novel therapeutic strategies. Across multiple studies, topical metformin formulations including simple topical solutions, nanoparticle-based systems, and hydrogel-based delivery platforms have consistently demonstrated anti-inflammatory, antioxidative and pro-regenerative effects.

Table 1. Summary of preclinical studies investigating topical metformin in diabetic wound models

Authors (Year)	Animal Model	Intervention	Key Molecular Effects	Healing Outcomes	Ref
Tombulturk et al. (2025)	STZ-induced diabetes; full-thickness excisional wound model	Topical Metformin (3 mM)	Increased AMPK expression; enhanced autophagy markers (LC3B, Beclin-1); modulation of hypoxia-related pathways	Improved wound repair and enhanced tissue regeneration under hypoxic conditions	[15]
Turhan et al. (2025)	STZ-induced diabetic Wistar rats with cutaneous wounds	Topical metformin gel compared with *Hypericum perforatum* extract	Improved fibroblast proliferation and reduced inflammatory response in wound tissue	Enhanced wound healing score and granulation tissue formation	[16]
Li et al. (2025)	STZ-induced diabetic rat full-thickness dorsal wound model	Topical manganese-based polyoxometalate nanozyme–metformin co-functionalized hydrogel (GPP-M@L)	Restored dendritic cell (DC) mitochondrial function; reduced ROS through SOD/CAT-like nanozyme activity; enhanced ATP production; activated PI3K–Akt signaling; suppressed NF-κB inflammatory pathway; increased GDF15-mediated DC–macrophage crosstalk; promoted macrophage M2 polarization and efferocytosis	Accelerated wound closure; enhanced angiogenesis and collagen deposition; improved extracellular matrix remodeling; restoration of immune homeostasis and improved diabetic wound regeneration	[17]
Xue et al. (2025)	Streptozotocin (STZ)-induced diabetic mice with infected full-thickness skin wound model	Photo-crosslinkable hyaluronic acid hydrogel containing ciprofloxacin-	Rapid ciprofloxacin release providing antibacterial activity; sustained metformin release modulating inflammation; reduced ROS levels; increased antioxidant enzyme activity (SOD, CAT, GPX);	Significant acceleration of wound closure; improved granulation tissue formation; enhanced tissue regeneration; effective	[18]

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		releasing crosslinker (PCA-CIP) and metformin-loaded PLGA nanoparticles (MET@NPs) with UV-triggered gelation	suppression of pro-inflammatory macrophage M1 polarization; downregulation of inflammatory cytokines (IL-1β, TNF-α, NOS2); promotion of anti-inflammatory macrophage phenotype and improved wound microenvironment	infection control; improved diabetic wound healing	
Yang et al. (2025)	STZ-induced diabetic mice with *Staphylococcus aureus*-infected full-thickness dorsal wounds	Metformin-containing nanoparticle microneedle patch	Activation of AMPK/SIRT1/PGC-1α axis; macrophage metabolic reprogramming	Accelerated healing, angiogenesis, and reduced scar formation	[19]
Luo et al. (2024)	Streptozotocin (STZ)-induced diabetic mice with infected full-thickness skin wound model	Microenvironment-responsive tannic acid–acrylic phenylboronic acid hydrogel loaded with metformin (ATAN-Met hydrogel)	ROS scavenging and antioxidant activity; inhibition of inflammatory pathways (↓TNF-α, ↓MMP9, ↓IL-6); promotion of macrophage polarization toward M2 phenotype (↑Arg1, ↑CD163; ↓iNOS, ↓CD86); activation of Hippo signaling pathway and metabolic regulation; enhanced angiogenesis markers (↑VEGF, ↑CD31); increased neurotrophic factor expression (↑NGF) and epithelial regeneration markers (↑α-SMA)	Accelerated wound closure; enhanced angiogenesis, epithelial regeneration, hair follicle regeneration, and nerve repair; reduced bacterial infection and inflammation; improved collagen deposition and tissue remodeling in diabetic wound model	[20]
Tombulturk et al. (2023)	Streptozotocin induced diabetes; full-thickness excisional wound model	Topical Metformin (3 mM)	Increased collagen I and III expression; reduced p53 and c-jun levels; anti-apoptotic effects	Enhanced fibroblast proliferation and accelerated wound healing	[12]
Zhu et al. (2023)	STZ-induced diabetic Sprague–Dawley rats; full-thickness infected dorsal wound model	Metformin-loaded CuPDA nanoparticles in hydrogel	Inhibition of NF-κB signaling and reduced nuclear translocation of p65; decreased expression of pro-inflammatory cytokines (↓TNF-α, ↓IL-6, ↓iNOS); increased anti-inflammatory markers (↑IL-10, ↑Arginase); ROS scavenging and reduction of oxidative stress; promotion of angiogenesis via activation of HIF-1α signaling with increased expression of VEGF, eNOS, Angiogenin, and KDR; macrophage phenotype modulation toward anti-inflammatory responses; antibacterial activity (>95% bacterial killing under NIR) and sustained Cu^{2+}-mediated antimicrobial effect	Accelerated wound closure in diabetic infected wounds; enhanced angiogenesis, fibroblast proliferation, and collagen deposition; reduced bacterial infection and inflammation; improved extracellular matrix remodeling and tissue regeneration in vivo	[21]
Zhang et al. (2023)	STZ-induced diabetic mouse model; full-thickness dorsal wound	Exosome/metformin-loaded self-healing conductive hydrogel (PEG/Ag/CNT-M + E hydrogel) containing ADSC-derived exosomes and metformin	Reduced ROS and mitochondrial ROS through inhibition of mitochondrial fission; downregulation of Drp1, Fis1, and Mff; upregulation of mitochondrial fusion proteins (Mfn1, Mfn2); suppression of inflammatory cytokines (↓IL-6, ↓TNF-α); decreased vascular inflammatory markers (↓ICAM, ↓VCAM); increased endothelial integrity (↑VE-cadherin); enhanced angiogenesis markers (↑CD31, ↑α-SMA); increased cellular proliferation marker Ki67; protection of F-actin homeostasis and endothelial function	accelerated wound closure in diabetic mice; improved re-epithelialization, granulation tissue formation, and collagen organization; enhanced angiogenesis and microvascular integrity; reduced inflammatory response and oxidative stress; improved endothelial cell proliferation, migration, and tube formation	[22]
Tombulturk et al. (2022)	STZ-induced diabetes; full-thickness excisional wound model	Topical Metformin-HCl (3 mM)	Suppressed NF-κB p65 activity; reduced RELA expression; decreased MMP-2 and MMP-9 expression	Accelerated wound closure and improved histological healing	[13]

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Mei et al. (2022)	STZ-induced type 2 diabetic mouse model; full-thickness dorsal skin wound	Metformin-loaded mesoporous silica nanoparticles embedded in silk fibroin hydrogel	Macrophage polarization toward M2 phenotype; inhibition of neutrophil extracellular traps; reduced inflammatory mediators	Enhanced angiogenesis, fibroblast migration, and wound healing	[23]
Zhu et al. (2022)	STZ-induced diabetic Sprague–Dawley rats; full-thickness dorsal excisional wounds	ROS-responsive PVA hydrogel delivering metformin and FGF21	ROS scavenging; recruitment of endothelial progenitor cells; increased Ang-1 expression	Enhanced angiogenesis and improved wound healing	[24]
Cam et al. (2021)	STZ-induced diabetic rat model	Topical nanofibrous scaffolds loaded with a combination of oral antidiabetic agents (metformin, pioglitazone, and glibenclamide) fabricated using electrospinning and pressurized gyration techniques	Reduced inflammatory cytokine expression, enhanced fibroblast proliferation, increased collagen deposition, improved extracellular matrix remodeling, and stimulation of angiogenic signaling pathways	Accelerated wound closure, enhanced re-epithelialization, improved dermal and epidermal regeneration, increased granulation tissue formation, and better histological organization of collagen fibers	[25]
El-Ridy et al. (2019)	STZ-induced diabetes; full-thickness dorsal wound	Transdermal metformin hydrochloride niosomal gel	Increased TGF beta 1 expression, reduced inflammatory cell infiltration and enhanced collagen synthesis	Improved re epithelialization and collagen deposition	[26]

Inflammation in Diabetic Wounds

Inflammation represents a critical phase in the normal wound healing process, functioning as an early defense mechanism against microbial invasion and tissue injury. Under physiological conditions, the inflammatory phase is tightly regulated and gradually transitions to the proliferative phase, allowing tissue repair and regeneration to occur. However, in diabetic wounds, this process becomes dysregulated and prolonged, leading to persistent inflammation that significantly impairs wound healing. Chronic hyperglycemia alters immune cell function, disrupts cytokine homeostasis, and promotes oxidative stress within the wound microenvironment, thereby preventing the normal progression of wound healing stages and contributing to the development of chronic wounds [27,28].

Generating hyperproduction of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β and interleukin-6, which is a signature of diabetic (mis)repair. These cytokines play key roles relevant to initiation of inflammatory responses, excessive or prolonged production is associated with continued infiltration and retention of inflammatory cells as well as unsuccessful attempts at tissue repair. High levels of these cytokines disrupt key cellular processes underlying wound healing, such as keratinocyte migration, fibroblast proliferation and extracellular matrix deposition. Consequently, diabetic wounds are often trapped in inflammatory phase of healing for extended amount of time and cannot naturally advance to the proliferative phase to regenerate tissues [4,29]. At the molecular level, nuclear factor-κB (NF-κB), a transcription factor, plays a key role in inflammation in diabetic wounds. When NF-κB signaling is activated, it triggers the transcription of several inflammatory mediators, such as cytokines, chemokines, and proteolytic enzymes that break down components of the extracellular matrix. Hyperglucemia-induced activation of the NF-κB cascade further enhances the inflammatory signaling pathway while suppressing the activity of growth factors essential for tissue regeneration. The resulting long-term activation of NF-κB is a major cause of chronic inflammation and poor healing in diabetes [30].

Oxidative stress is another important factor that makes diabetic wounds stay inflamed for a long time. Long-term high blood sugar levels cause problems with mitochondria and more ROS production, which damages cells and tissues around them. High amounts of ROS can also turn on inflammatory signaling pathways like NF-κB, which makes a cycle of oxidative stress and inflammation worse. This imbalance harms blood vessels and slows down wound healing by making angiogenesis and extracellular matrix remodeling less effective [31].

Moreover, the inflammatory environment of diabetic wounds is profoundly affected by immune cell dysregulation. During the proliferative phase of healing, macrophages generally transition from a pro-

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inflammatory M1 phenotype in the early inflammatory phase to an anti-inflammatory M2 phenotype. However, this phenotypic flip is frequently compromised in diabetic wounds, resulting in the continuous buildup of M1 macrophages and the continued generation of inflammatory mediators. The failure to adequately reduce inflammation ultimately hinders tissue repair and extends the chronicity of wounds [32].

These pathways collectively demonstrate that diabetic wound healing is characterized by a complex interplay of chronic inflammation, oxidative stress, and immunological dysfunction. Persistent activation of inflammatory pathways, heightened cytokine production, and the accumulation of reactive oxygen species (ROS) create a harmful wound milieu that impedes tissue healing. Consequently, treatment approaches focused on regulating inflammatory signals and reestablishing redox balance are crucial for enhancing healing outcomes in diabetic wounds.

Mechanisms of Topical Metformin in Diabetic Wounds

Newer data suggests that metformin has multiple immunometabolic and cytoprotective effects in addition to its initial hypoglycaemic effect. In this way, topical metformin could modulate the diabetic wound microenvironment either directly or through different molecular pathways involved with inflammation, oxidative stress and tissue regeneration via local administration. These coordinate actions lead to enhanced diabetic wound healing and restoration of tissue homeostatic balance [33].

The AMPK signaling pathway is one of the primary pathways through which metformin exerts its beneficial effects. AMPK is a master metabolic regulator that adjusts metabolic responses to various cellular stressors. AMPK activation improves mitochondrial function, restores the cellular energy status and initiates metabolic stress adaptive responses in the diabetic milieu. In contrast, metformin treatment has shown significant upregulation of autophagy associated markers in experimental studies over the years like LC3B and Beclin-1 level along with pAMPK activity higher degree level to promote tissue repair in diabetic wound healing leading toward increased survival [15]

Thus, the activation of AMPK exerted also potent anti-inflammation effect by blocking NF-κB pathway which is essential for inflammation gene transcription modulation. In diabetic wounds, pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 are continuously produced by long-standing activating of NF-κB that triggers chronic inflammatory response. Experiments showed that metformin has a topical effect, inhibiting NF-κB p65 activity and down-regulating inflammatory mediators in wound tissues. This opposite property restores immune balance in the wound microenvironment and promotes the transition from inflammation phase to proliferation phase of tissue reconstruction [13].

Another key mechanism whereby metformin promotes wound healing is through modulation of oxidative stress. Diabetic wounds feature high generation of reactive oxygen species (ROS) due to hyperglycemia-induced mitochondrial dysfunction and metabolic disruptions resulting in increased ROS production. Higher ROS levels induce cell damage and potentiate inflammatory signaling pathways. Metformin reduces ROS generation, making it an oxidative stress fighter to preserve mitochondrial homeostasis and protect endothelial cells and fibroblasts from oxidative damage by promoting normal cellular repair pathways [16].

Also, metformin contributes to extracellular matrix remodeling and tissue regeneration via its anti-inflammatory and antioxidant actions. Such studies indicated that metformin regulates the expression of collagen I and collagen III, which are essential for granulation tissue formation during wound healing, as well as fibroblast proliferation, thus promoting diabetic mouse wound repair. Concomitantly, metformin suppresses matrix metalloproteinases (MMP-2 and MMP-9), the enzymes responsible for excessive extracellular matrix degradation in chronic wounds. These synergistic effects help maintain extracellular matrix homeostasis and promote diabetic wound healing [13].

In addition, recent studies have presented data on immunomodulatory effect of metformin as a local-agent in wound microenvironment. In fact, this metformin-hydrogels based biomaterial systems (hydrogels & nanocomposite dressings) ability to sensitize macrophage re-programming toward M2 anti-inflammatory phenotype acts as one of the major factors in preventing inflammation-mediated tissue injury and contributing towards resolving inflammatory process to allow efficient tissue remodeling and wound repair. Such immunomodulatory effect promotes fibroblast migration, endothelial cell proliferation and angiogenesis which consequently lead to the regenerative-phase of wound healing [21].

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Integrated Mechanistic Insights from Preclinical Studies

There are four overlapping phases in the closely controlled biological process of wound healing: hemostasis, inflammation, proliferation, and remodeling. In diabetic wounds, ongoing hyperglycemia interferes with this process by maintaining inflammatory signals, provoking oxidative stress, and hindering cellular repair pathways, leading to chronic non-healing wounds. [34]. Increasing preclinical evidence suggests that topical metformin may improve diabetic wound healing by modulating several interconnected molecular pathways involved in inflammation, cellular metabolism and tissue regeneration.

Despite differences in experimental design and drug delivery platforms including conventional topical formulations, metformin-loaded hydrogels, nanocomposite dressings, and emerging exosome-based systems, most studies converge on a shared mechanistic framework in which metformin acts as a regulator of the pathological metabolic microenvironment in diabetic wounds. Instead of targeting a single pathway, metformin exerts multifactorial immunometabolic effects that restore cellular homeostasis and promote tissue repair.

The integrated molecular mechanisms through which topical metformin promotes diabetic wound healing are summarized in Figure 2. Collectively, current preclinical evidence demonstrates that topical metformin exerts pleiotropic therapeutic effects by simultaneously regulating inflammatory signaling, oxidative stress, macrophage polarization, angiogenesis, extracellular matrix remodeling, and tissue regeneration.

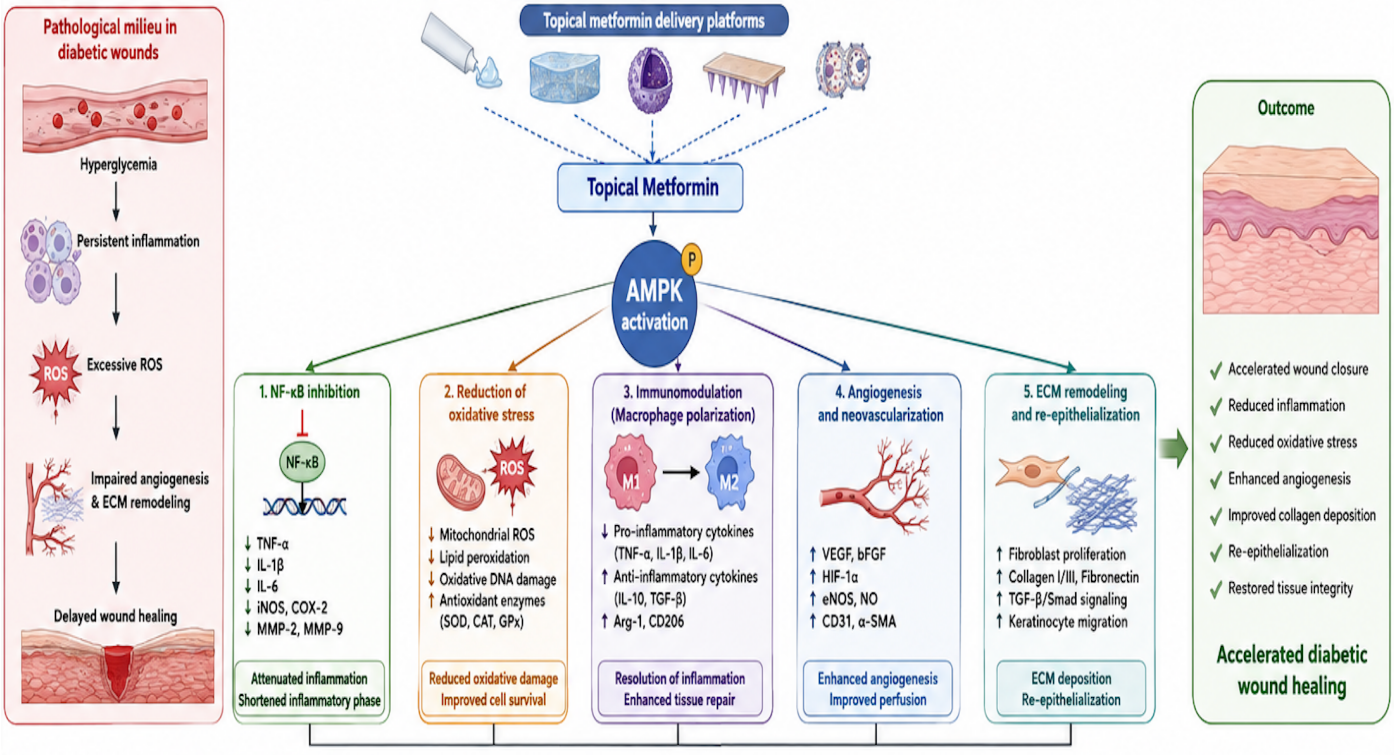

Figure 2. Integrated mechanistic framework of topical metformin in diabetic wound healing (Created in https://BioRender.com)
Topically delivered metformin activates AMP-activated protein kinase (AMPK), leading to inhibition of NF-κB signaling, attenuation of oxidative stress, macrophage polarization toward the M2 phenotype, stimulation of angiogenesis, and enhancement of extracellular matrix (ECM) remodeling and re-epithelialization. These coordinated effects reduce chronic inflammation and oxidative damage while promoting tissue regeneration, ultimately accelerating wound closure and restoring tissue integrity.
Abbreviations: AMPK, AMP-activated protein kinase; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; IL, interleukin; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; ECM, extracellular matrix.

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Table 2. Comparison of topical metformin delivery systems evaluated in diabetic wound healing

Delivery system	Representative studies	Metformin formulation	Drug release characteristics	Main biological effects reported	Limitation
Conventional topical solution/gel	Tombulturk *et al.* (2022, 2024, 2025); Turhan *et al*. (2025)	Topical metformin (3 mM gel)	Passive diffusion	Reduced inflammation, accelerated wound closure, increased collagen synthesis, enhanced autophagy, reduced apoptosis	Limited control over drug retention and sustained release.
Niosomal gel	El-Ridy *et al*. (2018)	Metformin HCl-loaded niosomes	Sustained release	Improved wound contraction and prolonged local drug availability	Limited evaluation of immune regulation and angiogenesis.
Nanofibrous scaffold	Cam *et al*. (2021)	Metformin-loaded scaffold (alone or combined with other antidiabetic drugs)	Sustained release	Enhanced collagen organization, dermal regeneration and reduced inflammatory infiltration	Some formulations included additional drugs, making individual contribution difficult to distinguish.
Injectable/self-healing hydrogel	Mei *et al*. (2022); Luo *et al.* (2024)	Metformin-loaded hydrogel	Controlled release responsive to wound microenvironment	Macrophage polarization, angiogenesis, antibacterial activity and tissue regeneration	Hydrogel composition differed substantially among studies.
ROS-responsive hydrogel	Zhu *et al*. (2022); Zhu *et al*. (2023); Xue *et al*. (2025)	Metformin incorporated into ROS-responsive hydrogel	Stimuli-responsive sustained release	Reduced oxidative stress, improved angiogenesis, antibacterial activity and accelerated wound repair	Several formulations co-delivered additional bioactive agents.
Exosome-based hydrogel	Zhang *et al*. (2023)	Exosome + metformin-loaded hydrogel	Sustained release	Improved angiogenesis, microvascular repair and reduced oxidative stress	Combination therapy prevents isolation of metformin-specific effects.
Nanozyme-based hydrogel	Li *et al*. (2025)	MnPOM nanozyme-metformin hydrogel	Controlled release	Enhanced efferocytosis, macrophage reprogramming and tissue regeneration	Multifunctional platform increases mechanistic complexity.
Microneedle system	Yang *et al*. (2025)	EGCG/metformin nanoparticle-loaded microneedles	Targeted transdermal delivery	Improved macrophage metabolic reprogramming, angiogenesis and scarless healing	Included another bioactive compound (EGCG).

Table 2 demonstrates the evolution of topical metformin delivery systems from conventional topical solutions and gels to increasingly sophisticated biomaterial-based platforms, including niosomes, nanofibrous scaffolds, hydrogels, microneedles, nanozyme-assisted hydrogels, and exosome-loaded hydrogels. Despite considerable differences in formulation design, all included studies consistently reported improved diabetic wound healing, primarily through suppression of inflammation, enhancement of tissue regeneration, increased collagen deposition, and accelerated wound closure. The earliest investigations mainly employed conventional topical metformin formulations to evaluate the intrinsic pharmacological activity of metformin. These studies consistently demonstrated inhibition of NF-κB signaling, downregulation of MMP-2 and MMP-9, enhanced collagen synthesis, reduced apoptosis, and activation of AMPK-mediated autophagy, providing direct evidence that metformin itself contributes to wound repair in STZ-induced diabetic animal models [12,13,15]. Subsequent research shifted toward advanced drug delivery platforms designed to overcome the limitations of conventional topical administration by improving local drug retention, sustaining drug release, enhancing skin penetration, and increasing local bioavailability. Niosomal formulations and nanofibrous scaffolds primarily improved prolonged drug release, whereas hydrogel-based systems introduced additional functions, including glucose- or ROS-responsive drug release, self-healing capability, tissue adhesion, injectability, and adaptability to the diabetic wound microenvironment [20–22,24,25].

More recently, multifunctional delivery platforms have combined metformin with biomaterials or additional bioactive agents, including silver nanoparticles, exosomes, FGF21, EGCG, ciprofloxacin, nanozymes, and functional hydrogel matrices. Besides improving drug delivery, these components possess intrinsic biological activities, such as antibacterial effects, ROS scavenging, immunomodulation, stimulation of angiogenesis, endothelial repair, extracellular matrix remodeling, and vascular regeneration. Consequently, these formulations generally demonstrated superior wound healing outcomes, including reduced inflammation and oxidative stress, enhanced macrophage polarization, increased angiogenesis,

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improved collagen deposition, stronger antibacterial activity, and accelerated tissue regeneration [17–19,21–24].

However, interpretation of these findings requires careful consideration. The included studies differed substantially in animal species, wound induction methods, metformin concentrations, formulation composition, treatment duration, and outcome measurements, limiting direct comparison among delivery platforms. More importantly, because most advanced formulations incorporated multiple bioactive materials together with metformin, the observed therapeutic benefits represent the overall performance of the multifunctional delivery system rather than the isolated pharmacological effect of metformin. For example, silver nanoparticles provide intrinsic antibacterial activity, exosomes possess regenerative and pro-angiogenic properties, FGF21 promotes endothelial repair, EGCG exhibits antioxidant and anti-inflammatory effects, nanozymes catalytically eliminate excessive ROS, and ciprofloxacin contributes potent antibacterial activity during early wound healing. Therefore, although these multifunctional systems consistently demonstrated improved therapeutic outcomes, the individual contribution of metformin cannot be clearly distinguished from that of the accompanying biomaterials or co-delivered therapeutic agents [17–19,21–24].

Similarly, improvements observed in several hydrogel-based systems may partly result from the physicochemical properties of the carrier itself. Biomaterial matrices protect metformin from premature degradation, prolong drug residence at the wound site, and enable controlled drug release in response to pathological stimuli such as hyperglycemia and oxidative stress. Accordingly, these findings should be interpreted as evidence supporting the efficacy of metformin-containing delivery systems, rather than definitive evidence of the pharmacological superiority of metformin alone [20,25,26]. Overall, current preclinical evidence supports the therapeutic potential of topical metformin-containing formulations for diabetic wound healing. Nevertheless, available evidence remains insufficient to determine the relative superiority of one delivery platform over another or to quantify the independent contribution of metformin within multifunctional formulations. Future studies should adopt standardized experimental protocols and incorporate appropriate comparator groups, including blank carriers, carrier-only controls, and bioactive agent-only formulations, to better distinguish the pharmacological effects of metformin from those of the delivery vehicle or accompanying therapeutic components. Such experimental designs would facilitate more robust comparisons among delivery platforms, strengthen mechanistic understanding, and improve the translational potential of topical metformin for future clinical application.

Translational Perspective and Limitations

Although the preclinical evidence consistently demonstrates that topical metformin-containing formulations accelerate diabetic wound healing, translating these findings into clinical practice remains challenging. All studies included in this review were conducted in experimental diabetic animal models, predominantly streptozotocin (STZ)-induced rodents, using different wound models, treatment durations, metformin concentrations, and delivery platforms. Such methodological heterogeneity limits direct extrapolation of the reported therapeutic outcomes to human diabetic wounds. Furthermore, differences in skin architecture, wound healing kinetics, immune responses, and diabetic pathophysiology between rodents and humans should be carefully considered when interpreting these preclinical findings.

Another important challenge concerns the clinical relevance of topical metformin dosage. The included studies employed a wide range of metformin concentrations and formulations, including 3 mM topical solution, 10% metformin gel, metformin-loaded nanoparticles, hydrogels, microneedles, and multifunctional biomaterial-based systems. Because these formulations differ substantially in drug loading, release kinetics, and local bioavailability, an equivalent clinically relevant topical dose has not yet been established. Consequently, additional pharmacokinetic and dose-optimization studies are required before translating these formulations into clinical application [16,19,23,26]. Systemic absorption following topical administration also remains insufficiently characterized. One of the theoretical advantages of topical metformin is the ability to achieve high local drug concentrations while minimizing systemic exposure. However, none of the included studies comprehensively evaluated systemic pharmacokinetics or circulating metformin concentrations after topical application. Therefore, although topical delivery is expected to reduce systemic exposure compared with oral administration, the extent of systemic absorption

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remains uncertain and warrants further investigation, particularly for formulations designed to enhance skin penetration, such as nanoparticles and microneedles [19,23,26].

Regarding safety, the available preclinical studies generally reported favorable local biocompatibility without evidence of delayed wound healing or significant local toxicity during the observation period. Nevertheless, the duration of most studies was relatively short and primarily focused on wound closure and histological improvement. Long-term safety, repeated-dose toxicity, local irritation, immunogenicity of advanced biomaterials, and potential systemic adverse effects remain largely unexplored. These considerations are particularly important for multifunctional delivery systems incorporating additional therapeutic components, such as silver nanoparticles, exosomes, nanozymes, antibiotics, or growth factors, which may introduce additional safety considerations beyond those associated with metformin alone [17,21–23].

Another important consideration is that most recently developed formulations combined metformin with biomaterials or additional bioactive agents to achieve multifunctional therapeutic effects. While these platforms consistently demonstrated improvements in antibacterial activity, oxidative stress modulation, macrophage polarization, angiogenesis, and extracellular matrix remodeling, the specific therapeutic contribution of metformin cannot always be distinguished from that of the carrier materials or co-delivered agents. Therefore, future studies should include appropriate comparator groups, such as blank carriers and carrier-only controls, to better define the pharmacological contribution of metformin within these multifunctional delivery systems. Overall, the current evidence supports the potential of topical metformin-containing delivery systems as promising therapeutic approaches for diabetic wound management. However, before clinical implementation can be considered, future investigations should focus on formulation standardization, optimization of clinically relevant topical dosing, pharmacokinetic evaluation of systemic absorption, comprehensive safety assessment, and well-designed randomized clinical trials to confirm efficacy and safety in patients with diabetic wounds.

CONCLUSION

Diabetic wounds are characterized by a complex interplay of chronic inflammation, oxidative stress, and impaired tissue regeneration, all of which contribute to delayed healing. Based on current preclinical evidence, topical metformin appears to play a significant role in modulating these underlying mechanisms. By activating AMPK signaling, suppressing inflammatory pathways such as NF-κB, and reducing oxidative stress, metformin supports key processes involved in tissue repair, including angiogenesis and collagen formation. In addition, the incorporation of metformin into advanced delivery systems, such as hydrogels and nanocomposites, has further enhanced its local effectiveness. Despite these promising findings, most evidence remains limited to experimental models. Therefore, further research involving standardized methods and clinical validation is necessary to fully establish its role in diabetic wound management.

AUTHOR CONTRIBUTIONS

Citra Safitri Wirman: Conceptualization, Writing original draft preparation, Data curation, Visualization. Benni Iskandar: Methodology, Formal Analysis. Darmawi Darmawi: Supervision, Validation, Review and Editing.

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