

# Mechanistic perspectives on the dermatologic potential of topical metformin: A scoping review

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**Abstract.** Metformin, a first-line anti-diabetic agent, has recently gained attention for its topical application in dermatology due to its pleiotropic pharmacological effects beyond glucose control. These include anti-inflammatory, antioxidant, anti-photoaging and wound-healing properties that suggest promising roles in skin health. The present scoping review aimed to map and synthesize existing experimental and clinical evidence on mechanistic pathways and the therapeutic potential of topical metformin in dermatologic applications. A comprehensive literature search was conducted across the Scopus, Web of Science, EBSCO, and PubMed databases for studies published between 2014 and 2024, using predefined inclusion criteria including key words, such as ‘topical metformin’, ‘topical metformin and skin aging’ and ‘topical metformin and dermatologic’. Data were extracted from 19 eligible studies, including *in vitro* and *in vivo* studies and clinical trials. The findings revealed that topical metformin inhibited melanogenesis by downregulating microphthalmia-associated transcription factor expression and related pathways, it promoted collagen synthesis and angiogenesis in wound models, and exerted anti-photoaging effects through oxidative stress modulation and enhanced autophagy. Additionally, it exhibited antitumor activity in melanoma and clinical efficacy in treating conditions, such as melasma and acne vulgaris with minimal adverse effects. Advanced delivery systems, such as hydrogels and nanofibers, have further improved the bioavailability and therapeutic outcomes. On the whole, as demonstrated herein, topical methods have emerged as a safe, multi-targeted agent with broad dermatological utility. Nevertheless, further well-designed clinical trials are

warranted to establish long-term safety, optimal dosage and formulation strategies for human use.

## Introduction

Metformin, a widely recognized oral anti-diabetic agent in the biguanide class, has historically been utilized as a foundational treatment for type 2 diabetes mellitus, particularly in contexts of limited resources or among patients without cardiovascular or renal complications (1). However, current international guidelines increasingly recommend glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors as preferred first-line therapies due to their additional cardiovascular and renal benefits (2). Despite this shift, metformin continues to attract attention owing to its pharmacological effects, which extend beyond glycemic regulation (3). Previous studies have revealed that metformin exerts anti-inflammatory, anti-fibrotic, antioxidant, anti-apoptotic and autophagy-inducing effects, many of which are potentially beneficial in dermatological applications, particularly through topical delivery systems (4-6).

In diabetic wound healing, where tissue repair is commonly delayed due to prolonged inflammation and impaired collagen deposition, topical metformin has shown promise in enhancing wound resolution (7). It activates AMP-activated protein kinase (AMPK), downregulates nuclear factor- $\kappa$ B (NF- $\kappa$ B) expression, and suppresses matrix metalloproteinase (MMPs; MMP-2 and MMP-9), thereby limiting inflammatory damage, preventing excessive apoptosis, and promoting collagen synthesis (8-11). It also enhances the activity of skin-resident stem cells and modulates proliferation-related markers such as c-Jun and p53, thereby contributing to improved re-epithelialization and dermal remodeling (12,13).

Metformin has also been shown to exert photoprotective effects in ultraviolet B (UVB)-induced skin injury models by inhibiting inflammatory mediators such as interleukin (IL)-1 $\beta$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and suppressing the nuclear translocation of CCAAT/enhancer-binding protein beta (C/EBP $\beta$ ), a key transcription factor involved in skin inflammation and activated p53 in UVB-damaged skin (14,15). Additionally, metformin increases autophagic activity and regulates apoptosis, thereby mitigating oxidative stress and cellular damage in photoaged skin (14,15).

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Topical metformin has also been evaluated in managing pigmentary conditions, such as melasma, with research demonstrating that it downregulates melanogenic proteins, including microphthalmia-associated transcription factor (MITF) and tyrosinase (16). Clinical trials have demonstrated that 30% metformin cream exhibits efficacy comparable to conventional triple combination creams (containing hydroquinone, tretinoin and fluocinolone), with fewer adverse effects, including reduced irritation and erythema (5,14). Furthermore, topical administration of metformin at concentrations of 1 and 10% in cream formulations effectively reduced clinical and histological signs of photoaging, attributed to its antioxidant, anti-inflammatory, anti-apoptotic, and autophagy-enhancing effects (4). Additionally, topical metformin hydrochloride hydrogels (concentrations of ~0.6%) have been shown to significantly improve wound healing, promoting rapid re-epithelialization and reducing inflammation in clinical studies involving traumatic wounds and cutaneous ulcers (8). Similarly, its use in acne vulgaris has demonstrated significant reductions in lesion counts, suggesting broader anti-inflammatory and sebo-suppressive properties (12). The drug's dermatological potential is further enhanced by advances in formulation technologies. Topical metformin has been successfully incorporated into hydrogels, nanofibers and vesicular systems, such as ethosomes, facilitating localized delivery and improved skin penetration (8,14).

Despite the increasing number of studies on topical metformin in various dermatological conditions, an integrative analysis that consolidates these findings into a mechanistic framework is lacking. Therefore, a comprehensive scoping review is essential to better understand the molecular pathways modulated by topical metformin and to assess its potential clinical applications. The present scoping review examines the mechanistic underpinnings and therapeutic relevance of topical metformin in dermatology based on *in vitro*, and *in vivo* studies, and clinical studies.

## Data and methods

Sources of information and data were obtained from literature available on the internet. A literature search was conducted by retrieving scientific research articles in electronic form using the EBSCO, Scopus, Web of Science and PubMed databases. The following key words were used: 'Topical Metformin', 'Topical Metformin and Skin Aging' and 'Topical Metformin and Dermatologic'. Articles were selected based on their relevance to the use of topical metformin in skin-related conditions. The authors assessed the eligibility of the results using predefined inclusion and exclusion criteria.

The included studies met the following criteria: i) The year of publication was between 2014 and 2024; ii) the study addressed topical metformin, skin aging, or dermatologic conditions; iii) topical metformin was used in the study; iv) the article was written in English. The exclusion criteria were as follows: i) Articles did not include a full-text description of the study; ii) the article was not written in English.

The study extracted data from each article regarding study characteristics (topical metformin or topical metformin related to skin aging), research objects or subjects (*in vitro*, animal models, or human participants), intervention methods,

treatment duration and main outcomes. The possible implications of each study for the dermatologic use of topical metformin were determined following data collection and analysis. The PRISMA flowchart of the study selection is presented in Fig. 1.

## Results and Discussion

A total of 891 records were identified from multiple databases, including EBSCO (127), Scopus (421), Web of Science (235) and PubMed (108). After removing duplicates, 452 records remained for screening. Following the initial screening of titles and abstracts, 319 records were excluded due to irrelevance. The remaining 133 full-text articles were assessed for eligibility based on the predefined inclusion criteria. Ultimately, 114 articles were excluded due to a lack of focus on topical metformin, being review articles, unavailability of full text, and irrelevance to skin aging and dermatologic conditions. The present scoping review included 19 eligible studies that examined the effects of topical metformin in dermatological applications. The findings are summarized in Table I and include *in vitro* and *in vivo* studies, and clinical investigations.

Multiple studies have demonstrated that topical metformin downregulates key pigmentation-related proteins such as MITF, tyrosinase, tyrosinase-related protein (TRP)1, and dopachrome tautomerase (DCT) in terms of anti-melanogenesis. These effects were observed in both human melanocytes and melanoma cells, with inhibition occurring via the suppression of cyclic adenosine monophosphate (cAMP)-cAMP response element-binding protein (CREB) signaling, independent of AMPK pathways (17,18). For anti-photoaging effects, topical metformin significantly reduced UVA- and UVB-induced oxidative stress and inflammation. This was evidenced by decreased malondialdehyde (MDA) levels, elevated glutathione (GSH), reduced IL-6 levels and the modulated expression of MMP-1 and collagen type I (COL-I) in preclinical models. The 10% topical metformin demonstrated histological improvements in skin structure and elasticity (4,19).

As regards its anticancer activity, topical metformin inhibited melanogenesis, suppressed the PI3K/Akt/mammalian target of rapamycin (mTOR) pathways, and reduced UV-induced DNA damage. Enhanced melanoma cell apoptosis and reduced tumor volume were observed in animal models (20,21). In wound healing, topical metformin accelerated re-epithelialization, reduced inflammation markers (TNF- $\alpha$  and IL-6), enhanced the collagen I/III ratios and promoted angiogenesis. The activation of autophagy through AMPK was noted as a key mechanism (6,10). The complete mechanistic perspectives are summarized in Table II. This table outlines the molecular mechanisms through which metformin exerts its effects, including the activation of key pathways such as AMPK, modulation of inflammatory cytokines, promotion of stem cell proliferation, and enhancement of tissue regeneration. These mechanisms collectively contribute to metformin's therapeutic potential in various skin regeneration and healing processes.

Existing studies on topical metformin have shown promising therapeutic effects in various dermatological applications. However, these findings have often been presented in isolation, with limited integration of the underlying molecular mechanisms. The present scoping review consolidates the current

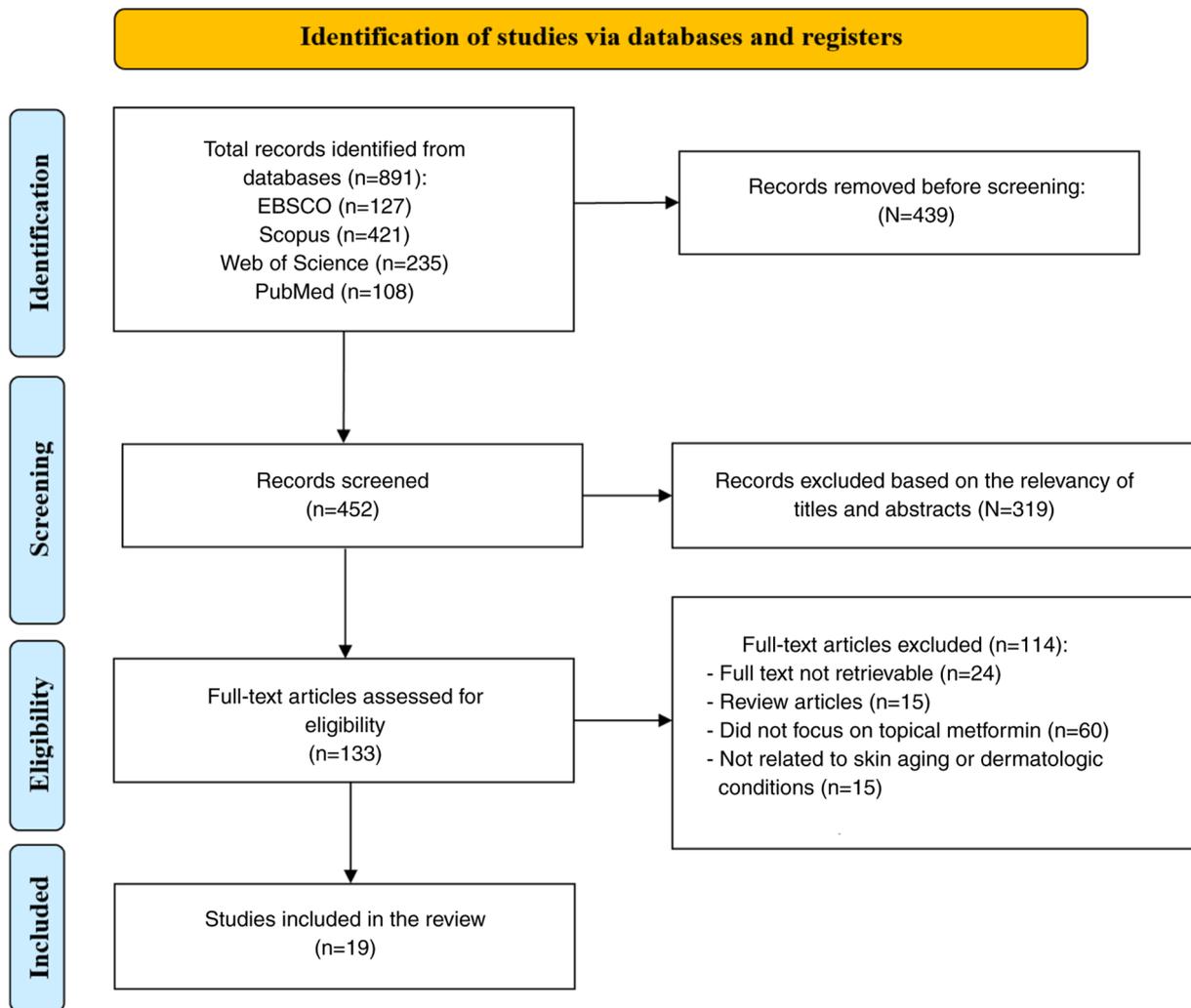


Figure 1. PRISMA flow diagram for the article selection process used in the present scoping review.

body of evidence, focusing on a mechanistic framework that links the diverse actions of topical metformin. One of the most striking features is the consistent activation of AMPK, a key regulator of cellular energy metabolism that plays a central role in mediating the anti-inflammatory, antioxidant, and anti-photoaging effects of metformin. AMPK activation downregulates inflammatory pathways such as NF- $\kappa$ B, reduces oxidative stress, and promotes collagen synthesis in wound healing and photoaged skin models (8,9). In addition to AMPK, topical metformin also affects autophagy, a cellular process involved in the degradation and recycling of damaged cellular components, which helps mitigate oxidative damage and improve skin cell turnover (4,5).

AMPK-independent pathways have also emerged as crucial components of the dermatological effects of metformin. For example, in melanogenesis, metformin inhibits cAMP/CREB/MITF signaling, leading to decreased melanin production, which highlights its potential in treating hyperpigmentation disorders (20,21). Additionally, its effects on PI3K/Akt/mTOR signaling are relevant in the context of skin photoaging, where suppression of this pathway contributes to reduced cellular senescence and oxidative stress (22). By integrating these mechanistic insights, the present scoping review

moves beyond a simple summary of clinical outcomes and provides a unified framework for understanding how topical metformin exerts its multi-faceted dermatological effects. The summarized mechanistic perspectives are presented in a conceptual diagram, as shown in Fig. 2.

*Potential of topical metformin as an anti-melanogenesis agent.* In line with an increase in UV exposure, the incidence of hyperpigmentation disorders in the elderly has increased. Preventive measures, such as sunscreen, topical or oral vitamins and antioxidants, remain one of the main options. However, other options, such as topical metformin, may also serve as a therapeutic choice, as it is non-toxic to normal cells, including melanocytes, keratinocytes, or fibroblasts. The study by Lehraiki *et al* (17) enhanced the mechanistic understanding of the role of topical metformin in modulating pigmentation pathways, underscoring its potential as a therapeutic candidate for hyperpigmentation disorders. Metformin decreases melanin synthesis in melanoma cells and normal human melanocytes by reducing cAMP levels and inhibiting CREB phosphorylation, leading to the downregulation of MITF and other key melanogenic genes such as tyrosinase, TRP1 and DCT. These effects occur independently of the AMPK pathway (17).

Table I. Summary of the studies on the potential effects of topical metformin for dermatological use.

First author, year of publication	Metformin form (concentration)	Study duration	Main objectives	Main findings	(Refs.)
<b>Anti-melanogenesis agent</b>					
Lehraiki, 2014	Solution (topical): 10 mM; <i>in vitro</i> : 5-10 mM)	Mice: 8 weeks; Humans: 15 days; <i>In vitro</i> : ≤72 h	To evaluate the effects of metformin on melanogenesis via the cAMP/CREB/MITF pathway.	Metformin significantly reduced melanin production by suppressing cAMP/CREB/MITF signaling, independent of AMPK activation.	(17)
Channakeshavaiah, 2019	Lotion (30%)	8 weeks	The study evaluated the safety and efficacy of 30% metformin lotion vs. TCC in melasma treatment.	Topical metformin is a safe, effective melasma treatment, showing comparable results to TCC with fewer side-effects.	(14)
AboAlsoud, 2022	Cream (30%)	8 weeks	The study compared 30 % metformin cream vs. TCC for melasma efficacy and safety.	Metformin significantly improved melasma with no side effects, making it a safe, effective alternative to TCC.	(5)
Ali Mapar, 2019	Cream (15%)	12 weeks	The study evaluated the efficacy of topical metformin for melasma treatment in a randomized clinical trial.	Topical metformin significantly reduced melasma without laboratory marker changes.	(23)
<b>Anti-skin cancer agent</b>					
Yu, 2019	Gel (4.81-5.32%)	10 days	The study evaluated transdermal metformin-loaded cubic phases for melanoma treatment <i>in silico</i> and <i>in vivo</i> .	Cubic gel significantly enhanced metformin delivery and exerted potent anti-melanoma effects.	(21)
Mousa, 2022	Metformin-loaded ethosomes	28 days	The study developed and evaluated a metformin-loaded ethosomal gel for treating chemically induced skin cancer in mice.	Metformin ethosomal gel significantly improved skin delivery and exerted antitumor effects without toxicity.	(20)
<b>Anti-photoaging agent</b>					
Xiao, 2021	Cream (0.6%)	72 h	The study investigated the protective effects of metformin against UVB-induced skin damage in mice.	Metformin significantly reduced inflammation and protected skin from UVB-induced damage.	(15)
Cui, 2019	Solution (0.01 mM)	72 h	The study assessed the effects of metformin on UVA-induced oxidative stress and gene expression in fibroblasts.	Metformin significantly reduced UVA damage, showing protective anti-photoaging effects.	(19)
Mostafa, 2022	Gel (1 and 10%); Oral (300 mg/kg)	10 weeks	The study evaluated topical and oral metformin ± CoQ10 on autophagy, oxidative stress, and apoptosis in photoaged mice.	10% topical metformin significantly improved photoaging; CoQ10 enhanced its protective effects.	(4)

Table I. Continued.

First author, year of publication	Metformin form (concentration)	Study duration	Main objectives	Main findings (Refs.)
<b>Wound healing</b>				
Zhao, 2017	Solution (2 $\mu$ M)	14 days	The study assessed topical metformin, resveratrol, and rapamycin on wound healing via AMPK activation in rodents.	Topical metformin significantly improved wound healing and regeneration via AMPK, outperforming resveratrol and rapamycin. (30)
Tombulturk, 2024	Gel (3 mM)	14 days	The study evaluated the effects of topical metformin on autophagy and hypoxia markers in diabetic rat wounds.	Topical metformin significantly improved diabetic wound healing by enhancing autophagy and stress adaptation. (31)
Qing, 2019	Metformin hydrochloride (topical gel, 100 $\mu$ mol/l and 200 $\mu$ mol/l)	14 days	The study investigated the role of metformin in accelerating wound healing via M2 macrophage polarization and AMPK/mTOR/NLRP3 pathway.	Topical metformin significantly enhanced diabetic wound healing by reducing inflammation and activating AMPK. (32)
Tombulturk, 2022	Solution (3mM)	14 days	The study investigated topical metformin's effect on diabetic wound healing via modulation of inflammatory pathways.	Topical metformin significantly improved diabetic wound healing by reducing inflammatory signaling and MMP expression. (11)
Cam, 2020	Nanofiber (4%)	14 days	The study evaluated the efficacy of metformin-loaded nanofibers on wound-healing <i>in vitro</i> and in diabetic rat models.	Metformin significantly improved wound healing and reduced TNF- $\alpha$ , but less than glybenclamide. (9)
Cam, 2021	Nanofiber (40 mg/ml)	14 days	The study evaluated metformin-loaded nanofiber scaffolds $\pm$ pioglitazone on diabetic wound healing in rats.	Metformin scaffolds improved wound healing, fibroblast growth, and reduced inflammation and edema. (33)
Tawfeek, 2020	Gel (0.6% Metformin-HCl)	Rats: 14 days; humans: 21-30 days	The study evaluated the efficacy of topical metformin hydrogel on wound-healing through pharmaceutical, preclinical, clinical, and histological analyses.	Topical metformin hydrogel significantly accelerated wound healing and regeneration in rats and humans. (8)
Zhang, 2024	Lotion (6%)	10 days	The study evaluated the effects of 6% topical metformin lotion on wound healing and scarring in rats.	Metformin lotion promoted scarless healing by modulating inflammation, collagen balance, and activating AMPK. (6)
Tombulturk, 2024	Solution (3 mM)	14 days	The study evaluated the proliferative and anti-apoptotic effects of topical metformin on wounds in diabetic and non-diabetic rats.	Topical metformin accelerated wound healing by enhancing collagen, proliferation, and reducing apoptosis markers. (10)
Xiong, 2022	Solution (300 mM)	29 days	The study evaluated the effects of topical metformin on stretched skin regeneration by assessing collagen, angiogenesis and stem cell activity.	Topical metformin significantly improved skin regeneration, thickness, collagen, angiogenesis, and stem cell proliferation. (13)

TCC, triple combination creams; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; MMP, mammalian target of rapamycin.

Table II. Summary of the mechanistic perspectives discussed in the studies included in the present scoping review.

First author, year of publication	Mechanistic perspectives	(Refs.)
<b>Anti-melanogenesis agent</b>		
Lehraiki, 2014	Metformin inhibits melanogenesis by lowering cAMP levels, which deactivates CREB and downregulates MITF, tyrosinase, and other melanogenic enzymes. This effect is independent of the activation of the AMPK pathway.	(17)
Channakeshavaiah, 2019	Metformin reduces cAMP accumulation and CREB phosphorylation, leading to decreased expression of MITF. In addition, it inhibits protein kinase C-beta (PKC- $\beta$ ), preventing its anchoring to melanosomes, thereby inhibiting melanogenesis.	(14)
AboAlsoud, 2022	Metformin inhibits melanogenic protein expression, such as tyrosinase and TRP-1, through a cAMP-dependent pathway, which is regulated by MITF.	(5)
Mapar, 2019	Topical metformin may suppress melanogenesis in melasma through cAMP inhibition and MITF downregulation, as well as AMPK pathway modulation.	(23)
<b>Anti-skin cancer agent</b>		
Yu, 2019	Metformin acts via both p21- and AMPK-independent pathways, promoting apoptosis and autophagy activation, which are associated with p53 and Bcl-2 modulation.	(21)
Mousa, 2022	The activation of AMPK by metformin, which inhibits the mTOR pathway, a key regulator of cancer cell proliferation, stemness, and survival. Ethosomes improve skin permeation using ethanol and isopropyl alcohol, which increase vesicle stability and reduce vesicle size, thereby enhancing metformin entrapment and release.	(20)
<b>Anti-photoaging agent</b>		
Xiao, 2021	Metformin inhibits UVB-induced inflammation in keratinocytes by suppressing proinflammatory cytokine transcription and secretion, such as IL-1 $\beta$ and TNF- $\alpha$ . This is achieved by downregulating C/EBP $\beta$ , a key transcription factor required for IL-1 $\beta$ expression and preventing its nuclear translocation.	(15)
Cui, 2019	Metformin decreases ROS levels, inhibits the expression of matrix metalloproteinases (MMP-1 and MMP-3), and increases the synthesis of type I collagen (COL-I), which is crucial for skin regeneration.	(19)
Mostafa, 2022	Metformin reduces oxidative stress by decreasing ROS, while also suppressing inflammatory markers such as IL-6 and MMP-1. In addition, metformin induces the expression of cathepsin D, a key autophagy protease, and reduces P62 accumulation, thereby improving skin regeneration and counteracting UV-induced damage.	(4)
<b>Wound healing agent</b>		
Zhao, 2017	Metformin increases p-AMPK and p-ACC expression, which are key components of the AMPK signaling cascade, thereby stimulating angiogenesis and collagen deposition in the wound beds.	(30)
Tombulturk, 2024	Metformin activates AMPK, enhancing autophagy by increasing LC3B and Beclin-1 expression, while reducing HIF-1 $\alpha$ levels under hypoxic conditions, promoting tissue regeneration and healing.	(31)
Qing, 2019	Metformin promotes wound healing by inducing macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This effect is mediated through the activation of AMPK and inhibition of the mTOR pathway, leading to the suppression of the NLRP3 inflammasome and decreased inflammation at the wound site.	(32)
Tombulturk, 2022	Metformin suppresses NF- $\kappa$ B p65 activity, a key regulator of inflammation, and significantly decreases the expression of the proinflammatory mediators MMP-2 and MMP-9, thereby promoting wound healing in diabetic rats	(11)

Table II. Continued.

First author, year of publication	Mechanistic perspectives	(Refs.)
Wound healing agent		
Cam, 2020	Metformin reduces the inflammatory cytokine TNF- $\alpha$ , which plays a significant role in the inflammatory phase of wound healing.	(9)
Cam, 2021	Metformin accelerates diabetic wound healing by modulating inflammatory cytokines and promoting fibroblast proliferation, likely through the inhibition of pro-inflammatory signaling pathways and modulation of vascularization, thereby facilitating faster wound closure.	(33)
Tawfeek, 2020	Topically applied metformin enhances wound healing by upregulating TGF- $\beta$ 1 expression, which in turn promotes angiogenesis, fibroplasia, and re-epithelialization, leading to faster wound closure and tissue regeneration. Metformin activates AMPK, inhibits TGF- $\beta$ 1, and reduces the number of myofibroblasts, leading to decreased collagen III production and increased collagen I expression. It also lowers the levels of the inflammatory markers HMGB1 and IL-1 $\beta$ , promoting the formation of scarless skin tissue during wound healing.	(8)
Zhang, 2024	Metformin increases the expression of collagen I and III, which are essential for wound repair, while reducing the expression of p53 and c-Jun, which are involved in apoptosis.	(6)
Tombulturk, 2024	Metformin enhances skin regeneration during mechanical stretching by improving the proliferative activity of skin-derived stem cells (ESCs and HFSCs), facilitating tissue regeneration, and enhancing the regenerative capacity of mechanically stretched skin.	(10)
Xiong, 2022	Metformin promoted mechanical stretch-induced skin regeneration by enhancing the proliferation of epidermal and hair follicle stem cells, increasing angiogenesis, and stimulating collagen synthesis. These effects were likely mediated through AMPK-related pathways that support stem cell activation, vascular remodeling, and extracellular matrix organization.	(13)

CREB, cAMP response element-binding protein; AMPK, AMP-activated protein kinase; cAMP, cyclic adenosine monophosphate; MITF, microphthalmia-associated transcription factor; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species; UVB, ultraviolet B.

Subsequent clinical observations have expanded this mechanistic foundation, investigating the significance of these pathways in the treatment of melasma. A previous preliminary clinical study evaluated the use of topical metformin in the treatment of melasma, outlining mechanistic pathways informed by earlier experimental research (14). The findings demonstrated that metformin reduced intracellular cAMP levels and CREB phosphorylation, thereby downregulating MITF, an essential regulator of melanogenesis. These cascades resulted in the decreased expression of critical melanogenic enzymes, including tyrosinase, TRP-1 and TRP-2. Metformin is suggested to impede the attachment of protein kinase C- $\beta$  to melanosomes, consequently interfering with melanin production through an alternative signaling pathway. The observed clinical improvements in patients with melasma treated with topical metformin correspond with these pathways, underscoring its potential as a safe and mechanistically validated depigmenting agent (14).

The study by AboAlsoud *et al* (5) further developed this clinical perspective through a randomized controlled trial, confirming the significance of the cAMP-MITF axis in depigmentation. The authors provided evidence that metformin lowers intracellular cAMP levels, leading to the deactivation

of CREB and the downregulation of MITF, a key regulator of melanogenesis. These cascades ultimately suppress the expression of melanogenic enzymes such as tyrosinase, TRP-1 and TRP-2. The observed clinical outcomes, particularly the notable decrease in MASI scores akin to that of the standard triple combination cream, underscore the therapeutic significance of these pathways. The mechanistic pathway was inferred from prior studies, and the trial reinforces the evidence supporting the role of topical metformin in inhibiting MITF-driven pigmentation (5).

Complementing these findings, Ali Mapar *et al* (23) provided additional clinical insights while also suggesting the involvement of the AMPK pathway. Referencing earlier preclinical findings, the authors of that study noted that metformin may reduce intracellular cAMP levels, thereby downregulating MITF, a central regulator of melanogenesis. Such a suppression is associated with lower expression levels of melanogenic enzymes, such as tyrosinase, TRP-1 and TRP-2. Additionally, metformin has been linked to the modulation of the AMPK pathway, which may contribute to its broader regulatory effect on melanin synthesis. While the clinical trial focused on efficacy outcomes measured through MASI scores, the trend of continued improvement over 12 weeks supports

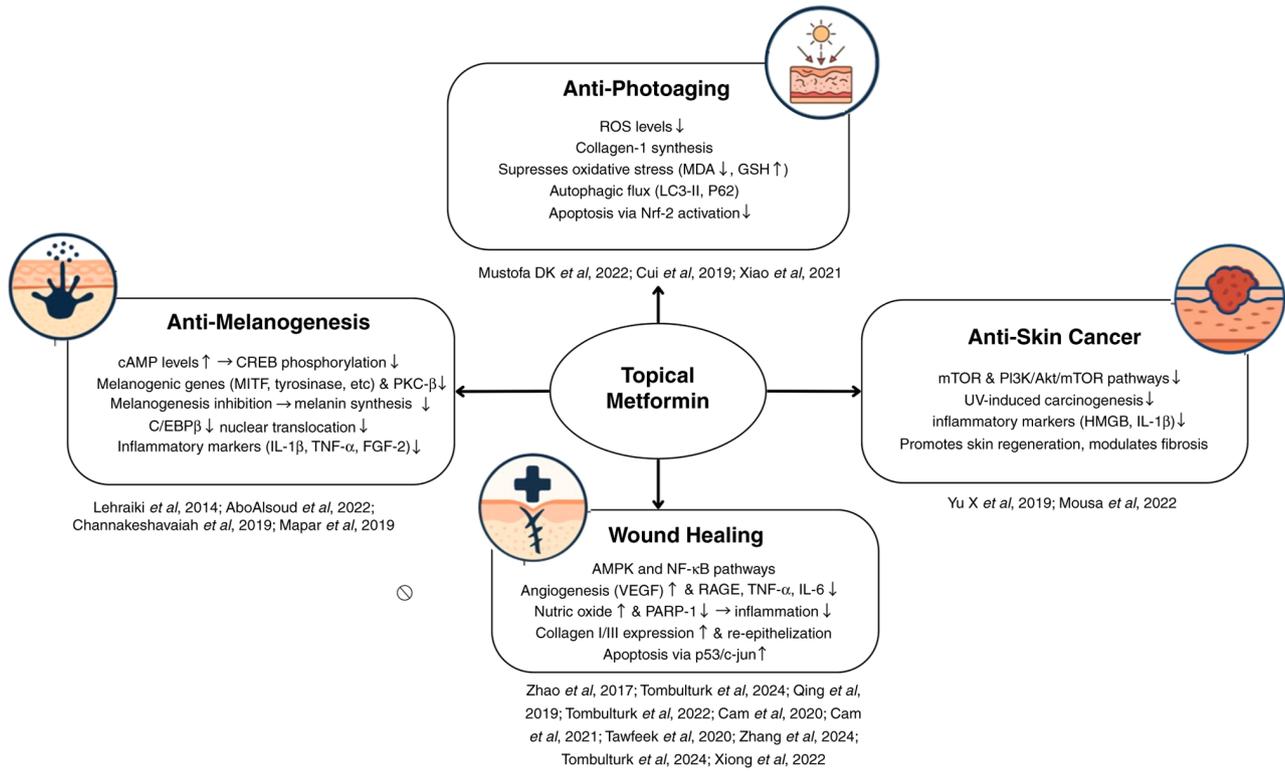


Figure 2. Mechanistic perspectives on the dermatologic potential of topical metformin. cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; MITF, microphthalmia-associated transcription factor; PKC-β, protein kinase C-β; IL, interleukin; TNF, tumor necrosis factor; FGF, fibroblast growth factor; ROS, reactive oxygen species; MDA, malondialdehyde; GSH, glutathione; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; VEGF, vascular endothelial growth factor; PARP-1, poly(ADP-ribose) polymerase 1; RAGE, receptors for advanced glycation end products. The studies mentioned in this figure are as follows: Lehraiki *et al.* (17), AboAlsoud *et al.* (5), Channakeshavaiah *et al.* (14), Mapar *et al.* (23), Mostafa *et al.* (4), Cui *et al.* (19), Xiao *et al.* (15), Yu *et al.* (21), Mousa *et al.* (20), Zhao *et al.* (30), Tombulturk *et al.* (31), Qing *et al.* (32), Tombulturk *et al.* (11), Cam *et al.* (9), Cam *et al.* (33), Tawfeek *et al.* (8), Zhang *et al.* (6), Tombulturk *et al.* (10), Xiong *et al.* (13).

the relevance of these mechanistic insights and underscores the therapeutic promise of topical metformin in pigmentary disorder (23).

#### Potential of topical metformin as an anti-skin cancer agent.

Metformin supports anticancer therapy by activating the liver kinase B1-AMPK pathway to inhibit gluconeogenesis in hepatocytes (24). This pathway inhibits mTOR and protein synthesis (25). Patients with cancer often have a p53 gene mutation, resulting in an unchecked cell cycle, even during hyperplasia, progressing to the dysplasia stage (26). A checkpoint exists between DNA synthesis and the mitotic phase to recognize and repair DNA damage (27). To assess the therapeutic potential of transdermal metformin-loaded cubic phases for melanoma treatment, Yu *et al.* (21) found that the topical application of metformin in a cubic phase gel significantly enhanced skin permeability and exhibited strong antitumor effects. A summarized overview of the anticancer mechanisms of metformin is illustrated in Fig. 2, with a more detailed depiction of its potential direct and indirect effects as an anticancer agent illustrated in Fig. 3. The unique structure of the cubic phase system, with its thermodynamically stable and lipid-rich matrix, enabled deeper skin penetration and prolonged metformin release, resulting in significant tumor growth inhibition and improved apoptotic activity *in vivo*. In addition to enhanced transdermal distribution, metformin has been demonstrated to trigger various cell death pathways

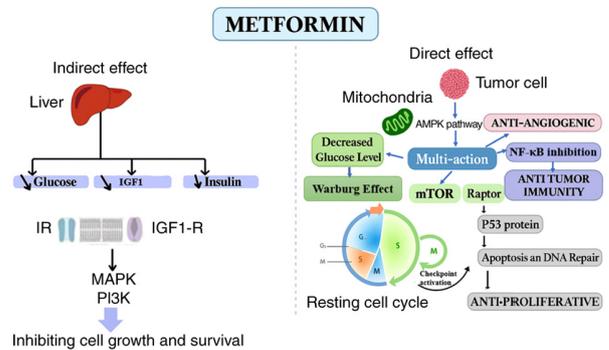


Figure 3. Potential mechanism of topical metformin as an anti-cancer agent.

via p-21 and AMPK-independent processes, resulting in apoptosis and autophagy (21). These effects are mediated by the activation of the tumor suppressor p53 and down-regulation of anti-apoptotic Bcl-2, indicating that metformin may exert significant anti-melanoma effects via different intracellular targets, independent of typical metabolic stress mechanisms (21).

In addition to these results, Mousa *et al.* (20) demonstrated the therapeutic potential of transdermal metformin administration by using the ethosomal gel technique to treat skin cancer. Unlike cubic phases, the ethosomal formulation utilizes ethanol and isopropyl alcohol to destabilize the

stratum corneum and increase vesicle fluidity, resulting in improved skin permeability, smaller vesicle size and greater metformin entrapment efficiency. In this model, the anticancer effect of metformin was predominantly due to AMPK activation, and the consequent suppression of the mTOR signaling pathway was a major regulator of cancer cell proliferation, stemness and survival. The combined evidence from both studies (20,21) demonstrates that distinct transdermal delivery platforms, whether through cubic phases or ethosomes, not only optimize the skin absorption of metformin, but also enable it to act through complementary molecular pathways, rendering these systems promising non-invasive strategies for the management of melanoma and other skin cancers (20).

#### *Potential of topical metformin as an anti-photoaging agent.*

Long-term exposure to the sun is the most common cause of photoaging, where the mutual interplay between autophagy, oxidative stress and apoptosis is implicated (28). In combating photoaging, pharmacological and natural ingredients that modulate autophagy are currently gaining more attention. Among these emerging agents, metformin has shown promising anti-photoaging properties (29). The general pathways through which metformin prevents photoaging are briefly summarized in Fig. 2. Metformin exerts anti-inflammatory and cytoprotective effects against UVB-induced skin injury in keratinocytes and mice. UVB irradiation typically induces inflammation and cell death by increasing the secretion of cytokines such as IL-1 $\beta$ , TNF- $\alpha$  and fibroblast growth factor-2. Metformin treatment significantly reduced the expression of these inflammatory markers at both the transcriptional and protein levels, partly by inhibiting the nuclear translocation of C/EBP $\beta$ , a transcription factor responsible for IL-1 $\beta$  production, leading to an anti-inflammatory effect (15). Metformin therapy preserved epidermal architecture, minimized keratinocyte apoptosis and significantly reduced the IL-1 $\beta$  and TNF- $\alpha$ , both at the transcript and protein levels, according to the study by Xiao *et al* (15). Additionally, metformin protected keratinocytes from UVB-induced cell death, not only by blocking direct damage but also by reducing deleterious paracrine factors. The topical application of 0.6% metformin cream in mice mitigated UVB-induced skin damage, decreased inflammatory cell infiltration and improved tissue histology, suggesting the potential of metformin as a topical agent for photoprotection and treatment of UV-induced skin damage. Metformin decreased UVB-induced inflammatory signaling and oxidative damage by modifying this upstream regulatory mechanism, indicating its potential as a prophylactic medication against photo-induced skin injury (15).

These tissue-level protective benefits are confirmed by *in vitro* evidence of the capacity of metformin to reduce UVA-induced oxidative stress in dermal fibroblasts. Cui *et al* (19), in a comparable *in vitro* model, demonstrated that metformin effectively reduced UVA-induced oxidative stress in human skin cells. The reactive oxygen species (ROS) content in the UVA group was considerably higher ( $P < 0.05$ ) than that in the control group. However, the ROS content in the UVA + metformin group was lower ( $P < 0.05$ ) than that in the UVA group (19). According to these findings, topical metformin may exert a preventive effect against photoaging by increasing COL-1 synthesis and reducing intracellular ROS

synthesis. The therapy reduced ROS levels and downregulated MMP-1 and MMP-3, enzymes involved in the degradation of the dermal extracellular matrix. At the same time, metformin increased the expression of COL-I, a critical structural component of the skin. These molecular alterations indicate that metformin not only shields cells from oxidative stress, but also promotes matrix preservation and regeneration, supporting its position as a potential anti-photoaging agent across both *in vitro* and *in vivo* settings (19).

Topical metformin exerts a comprehensive preventive effect against skin aging, including enhanced protection against UVA-induced photoaging. The study by Mostafa *et al* (4) using a mouse model investigated the potential of repurposing metformin to combat UVA-induced photoaging by modulating autophagy, oxidative stress, and apoptosis in the skin (4). That study revealed that topical treatment with 10% metformin significantly improved skin elasticity and histological structure, reduced oxidative stress (as indicated by decreased MDA and increased GSH levels), reduced inflammation (decreased IL-6), and suppressed collagen breakdown (reduced MMP-1) (4). The enhancement was linked to an increase in autophagic flux by upregulating cathepsin D and modulating LC3-II and p62 levels, thereby reversing the blockade of UVA-induced autophagy. In addition, metformin diminished apoptosis and restored antioxidant capacity, partly through the activation of nuclear factor erythroid 2 (Nrf-2). The benefits were further boosted when paired with coenzyme Q10 (CoQ10), indicating a synergistic interaction. CoQ10 amplified the protective effects of metformin, particularly in keratinocytes, supporting its combined use as a promising therapeutic strategy against photoaging. Furthermore, the activation of AMPK and the inhibition of the mTOR pathway were recognized as pivotal biochemical processes supporting metformin's protective effects. The use of ethosomal gel formulation enabled efficient skin penetration and sustained drug release, supported by ethanol and isopropyl alcohol, which improved vesicle stability and metformin encapsulation (4).

#### *Potential of topical metformin as a wound-healing agent.*

Topical application of metformin could shorten the duration of wound healing by inhibiting several inflammatory pathways, as summarized in Fig. 2. The two main inflammatory mechanisms blocked by topical metformin are the AMPK and NF- $\kappa$ B pathways (Fig. 4). This effect was reported by Zhao *et al* (30), who found that the chronic local application of metformin led to the increased expression of p-AMPK and its downstream target phosphorylated acetyl-CoA carboxylase, both of which are central to the AMPK signaling cascade. This molecular activation was closely associated with improved angiogenesis, as evidenced by increased CD31<sup>+</sup> endothelial structures and enhanced collagen deposition in the wound beds. These effects were particularly pronounced in aged skin, where metformin effectively reversed age-related AMPK suppression and vascular deficiencies, ultimately accelerating wound closure and restoring cutaneous integrity. These findings provide compelling evidence that topical metformin promotes regenerative processes in cutaneous wounds by stimulating AMPK-mediated angiogenesis and matrix remodeling (30).

The wound healing process includes hemostasis, inflammation, proliferation, and remodeling. In addition to the

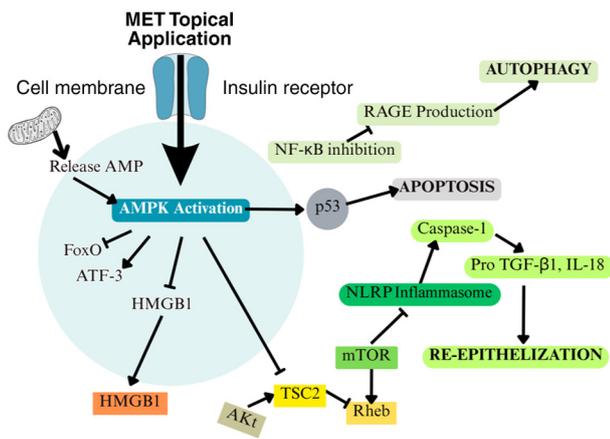


Figure 4. Potential mechanisms of topical metformin in wound healing.

angiogenesis stage, metformin regulates intracellular repair processes during wound healing, including autophagy and adaptation to hypoxia. Topical metformin appears to enhance wound healing in diabetic conditions by modulating key cellular mechanisms involved in autophagy and the hypoxic response. The research conducted by Tombulturk *et al* (31) revealed that metformin stimulated AMPK signaling, hence markedly enhancing the expression of autophagy markers LC3B and Beclin-1 in wound tissues. This autophagic response enhanced re-epithelialization and tissue regeneration by fostering cellular survival, proliferation and migration. Simultaneously, metformin administration resulted in a significant decrease in HIF-1 $\alpha$  levels under hypoxic circumstances, indicating a regulatory function in sustaining cellular homeostasis throughout the healing process. Collectively, these data substantiate the mechanistic perspective that AMPK-mediated autophagy activation, in conjunction with the control of hypoxia-related pathways, underpins the therapeutic efficacy of topical metformin in addressing delayed wound healing in patients with diabetes (31).

Concurrently, immunological regulation is a vital component of the mechanisms of metformin, particularly via alterations in macrophage phenotype. Qing *et al* (32) demonstrated that the topical administration of metformin markedly accelerated wound healing in diabetic mice, primarily by influencing the inflammatory response via macrophage polarization. Metformin therapy facilitated a phenotypic transition from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages at the wound site, correlating with improved tissue regeneration and re-epithelialization (32). This immunomodulatory impact was mechanistically achieved by the activation of AMPK, a crucial metabolic sensor, which subsequently suppressed the mTOR signaling pathway. mTOR inhibition resulted in the decrease of NLRP3 inflammasome activation, a key contributor to persistent inflammation in diabetic wounds. Consequently, the generation of inflammatory cytokines was reduced, fostering a milieu favorable for tissue repair. These results highlight the function of metformin in facilitating macrophage-mediated resolution of inflammation and enhancing wound healing via the AMPK/mTOR/NLRP3 pathway. The topical application of metformin enhanced autophagy via the activation of the AMPK pathway. This

condition suppresses the production of receptors for advanced glycation end products, inhibits NF- $\kappa$ B, TNF- $\alpha$ , and IL-6, and increases angiogenesis by releasing von Willebrand factor and vascular endothelial growth factor (32).

Metformin also increases nitric oxide production and inhibits the poly (ADP-ribose) polymerase 1 pathway through the AMPK pathway, resulting in a reduced inflammatory response. This immunomodulatory effect enhances the inhibition of traditional pro-inflammatory mediators in chronic wounds by metformin. The research conducted by Tombulturk *et al* (11) provides substantial data about the mechanism of topical metformin in wound healing, illustrating its anti-inflammatory activity via the modulation of NF- $\kappa$ B signaling. Metformin notably inhibited NF- $\kappa$ B p53 activity and diminished the mRNA expression levels of its downstream targets, MMP-2 and MMP-9, which are MMPs frequently overexpressed in chronic diabetic wounds and play a role in extracellular matrix degradation and compromised tissue repair. By downregulating this inflammatory cascade, metformin promotes the resolution of the extended inflammatory phase often observed in diabetic wounds, therefore allowing advancement into the proliferative phase of healing. The molecular effects align with the reported clinical consequences of expedited wound healing, establishing metformin as a potential therapeutic drug for enhancing tissue regeneration in diabetes-compromised cutaneous wounds (11).

Consistent with these findings, Cam *et al* (9) further demonstrated the capacity of metformin to inhibit TNF- $\alpha$  expression in diabetic wounds. Topically delivered metformin demonstrated anti-inflammatory effects in diabetic wound healing by significantly lowering the expression of TNF- $\alpha$ , a pivotal cytokine involved in sustaining the inflammatory phase of wound repair. In that study, diabetic rats treated with metformin-loaded bacterial cellulose/gelatin nanofibers exhibited a marked reduction in TNF- $\alpha$  levels by day 14, which corresponded with improved histological outcomes, including enhanced re-epithelialization and granulation tissue organization (9). Since TNF- $\alpha$  is known to delay wound progression by perpetuating macrophage-mediated inflammation, its suppression by metformin suggests a beneficial modulation of the early immune response, ultimately supporting tissue regeneration and accelerated healing in hyperglycemic conditions. These findings reinforce the therapeutic relevance of the anti-inflammatory properties of metformin in resolving chronic inflammation, a major barrier to effective wound closure in diabetic patients (9).

Moreover, metformin has been shown to support fibroblast proliferation and the development of granulation tissue. Cam *et al* (33) demonstrated that topical metformin significantly enhanced diabetic wound healing by modulating inflammatory cytokines and promoting fibroblast-mediated tissue repair. In that study, wounds treated with metformin-loaded gelatin nanofiber scaffolds exhibited accelerated re-epithelialization and contraction, accompanied by reduced levels of proinflammatory markers such as TNF- $\alpha$ . This suggests that metformin may act by inhibiting proinflammatory signaling pathways, creating a microenvironment conducive to tissue repair (33). Additionally, histological analysis revealed increased fibroblast proliferation and an improvement in the development of granulation tissue, indicating enhanced cellular regeneration.

The porous structure of the scaffold also supported vascularization, further facilitating the delivery of oxygen and nutrients essential for wound closure. These combined effects highlight the multifaceted role of metformin in promoting tissue regeneration in diabetic wounds by suppressing inflammation and supporting structural healing processes (33).

In addition to its effects on fibroblasts and inflammation, metformin may also regulate fibrogenic signaling via TGF- $\beta$ 1. The topical application of metformin hydrochloride hydrogel has been shown to significantly accelerate wound healing by upregulating TGF- $\beta$ 1, a pivotal cytokine in tissue regeneration. In the study by Tawfeek *et al* (8), immunohistochemical analysis revealed a marked increase in TGF- $\beta$ 1 expression in treated wounds, particularly within fibroblasts, compared to baseline levels. This molecular enhancement was associated with the histological evidence of robust angiogenesis, fibroplasia and the complete re-epithelialization of the wound bed (8). Elevated TGF- $\beta$ 1 signaling is known to facilitate vascularization, stimulate extracellular matrix production, and promote keratinocyte migration, collectively contributing to faster wound closure and tissue remodeling. These findings provide valuable mechanistic support for the therapeutic use of topical metformin in cutaneous wound management, especially in cases where enhanced regenerative response is critical (8).

Notably, the suppression of TGF- $\beta$ 1 by metformin has also been linked to scarless wound healing. Topical methods have demonstrated significant potential in promoting scarless skin wound healing by modulating multiple fibrotic and inflammatory pathways. The study by Zhang *et al* (6) demonstrated that metformin activates AMPK, a central energy-sensing enzyme, which in turn leads to the downregulation of TGF- $\beta$ 1, a key pro-fibrotic cytokine. This suppression of TGF- $\beta$ 1 was associated with a marked reduction in the number of  $\alpha$ -SMA-positive myofibroblasts, cells known to drive extracellular matrix deposition and fibrosis. Consequently, there was a decrease in collagen III expression, typically linked to disorganized scar tissue, and a concurrent increase in collagen I, indicative of organized tissue regeneration. Furthermore, metformin treatment significantly reduced the levels of pro-inflammatory markers HMGB1 and IL-1 $\beta$ , thereby contributing to an anti-inflammatory microenvironment favorable for healing. These findings support the mechanism whereby metformin, through AMPK activation and inflammatory suppression, fosters the development of functional, scar-free skin tissue (6).

Further supporting this finding, metformin promotes wound repair by balancing collagen synthesis and inhibiting apoptosis. According to the study by Tombultürk *et al* (10), the application of topical metformin enhanced wound healing in both diabetic and non-diabetic Wistar rats by exerting pro-proliferative and anti-apoptotic effects. Treated wounds exhibited faster closure and improved histological organization, which was associated with increased levels of collagen types I and III, key structural proteins involved in tissue regeneration. Additionally, metformin reduced the expression of the apoptosis-related proteins p53 and c-Jun, suggesting a decrease in programmed cell death within the wound area. These findings indicate that metformin supports the healing process by stimulating collagen production and cell proliferation while limiting apoptosis, ultimately improving

wound repair outcomes across different metabolic conditions (10).

Finally, the regenerative benefits of metformin have also been explored in mechanically stressed skin models, where stem cell activation plays a key role. Xiong *et al* (13) found that applying topical metformin notably improved the regenerative response in mechanically stretched skin in rats. The treatment resulted in a marked increase in both epidermal and dermal thickness, accompanied by greater collagen accumulation and enhanced formation of new blood vessels. Moreover, metformin stimulated the proliferation of key skin-derived stem cells, including epidermal stem cells and hair follicle bulge stem cells, which play a crucial role in skin repair. These outcomes suggest that metformin enhances the regenerative potential of stretched skin by enhancing stem cell activity, promoting tissue remodeling, and reinforcing the structural and vascular components essential for effective skin regeneration (13).

*Topical metformin for other dermatological uses.* Topical metformin has shown promising potential for managing various dermatologic conditions, particularly acne vulgaris, psoriasis, and alopecia, by targeting both inflammatory and metabolic pathways. Emerging research has identified metformin as a potential topical agent for acne due to its diverse pharmacological actions beyond glucose control. If delivered through the skin, metformin demonstrates anti-inflammatory, lipid-reducing (sebo-suppressive), and antioxidant activities that directly address the key pathological elements of acne (34). Metformin reduces lesion severity by modulating insulin resistance, androgen levels and local inflammation, primarily through the inhibition of the NF- $\kappa$ B signaling pathway and the suppression of pro-inflammatory cytokines, such as IL-6 and TNF- $\alpha$ . Its topical application has been shown to improve clinical outcomes with minimal irritation, offering a safe alternative or adjunct to traditional acne therapies (12). In psoriasis, metformin acts through the AMPK/mTOR signaling axis to inhibit keratinocyte hyperproliferation, suppress oxidative stress, and promote apoptosis in overactive epidermal layers (35). These effects are particularly beneficial in patients with comorbid metabolic syndrome, as metformin also helps regulate glucose and lipid metabolism. As regards alopecia, recent studies suggest that metformin may support hair follicle regeneration by enhancing perifollicular angiogenesis and suppressing perifollicular inflammation, although more data are needed to confirm this benefit (36). Collectively, these findings highlight the versatility and mechanistic depth of metformin as a topical treatment for chronic skin disorders characterized by dysregulated immune or metabolic activity.

*Clinical relevance and translational perspectives.* Recent clinical trials have highlighted the therapeutic potential of topical metformin in dermatology. A 30% metformin cream has shown efficacy in treating melasma, with results comparable to conventional treatments but fewer adverse effects, such as irritation or erythema (5). Similarly, a 0.6% hydrogel for wound healing demonstrated the ability to accelerate tissue regeneration, enhance collagen synthesis, and reduce inflammation (7). These studies support the promising role of topical metformin in managing conditions, such as hyperpigmentation and chronic wounds, particularly in diabetic patients.

Recent innovations in topical drug delivery have been explored to address the limited skin permeability of metformin due to its hydrophilic nature and high polarity. These advanced formulations allow for more targeted and sustained drug release within the sebaceous units, thereby improving therapeutic outcomes and minimizing systemic exposure (8). Mousa *et al* (20) found that ethosomal gels significantly increased metformin's skin bioavailability, and other formulations, such as nanofibers and hydrogels, have also shown promise in improving localized drug delivery (8,20). Although these formulations have proven to be safe in clinical trials with minimal adverse effects, further research is needed to assess the long-term safety and optimal dosing of topical metformin, especially for broader patient populations and more chronic use.

In conclusion, the main purpose of metformin is to treat type 2 diabetes. In the present scoping review, it was demonstrated that metformin is a potential topical treatment for wound healing, melanoma, and UVA- and UVB-induced aging of the skin, in addition to being an oral anti-diabetic drug. This information has been used to evaluate the possible modes of action of each effect. Topical metformin has anti-melanogenic properties on human skin biopsies and epidermis. It also possesses anti-inflammatory, anti-apoptotic, antioxidant, and anti-photoaging properties. Topical metformin was previously shown to function only as an antagonist in pigmentation in animal studies (37); nevertheless, there have recently been hopeful reports in cutaneous malignancies and hyperpigmentation diseases, including melanoma (21).

In preclinical studies, topical metformin has demonstrated promising therapeutic potential for various dermatologic conditions, including wound healing, hyperpigmentation, and UV-induced skin photoaging. However, the majority of these findings are based on experimental models (*in vitro* and *in vivo*). Consequently, further research in clinical trials is required to determine appropriate dosage, safety, and efficacy, as well as to identify the most effective lead compounds for human use through high-throughput analysis.

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### Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

### Authors' contributions

All authors (EN, JWG and MH) conceptualized the study. EN conducted the literature search, drafted the initial manuscript, and prepared the figures. JWG and MH provided supervision,

revised the manuscript, and finalized the final version of the manuscript. EN and JWG confirmed the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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