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Topical Metformin In Dermatology: A Narrative Review Of Efficacy And Formulation Approaches

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ABSTRACT

Metformin, a well-established first-line oral antidiabetic agent, has recently attracted interest in dermatology because of its anti-inflammatory, antioxidant, and regenerative properties. The skin, being vulnerable to aging and environmental damage, is a promising target for topical metformin therapy, although its clinical translation remains limited. This narrative review critically examines current evidence on topical metformin in dermatological applications and explores formulation approaches to optimize its cutaneous delivery. A thematic literature search was conducted in PubMed, Scopus, ScienceDirect, and Google Scholar for articles published between 2015 and 2025, focusing on studies of topical metformin for skin disorders. The final selection included 13 articles on wound healing, 5 on melasma, 1 on acne, 1 on psoriasis, and 1 on alopecia, all meeting predefined inclusion and exclusion criteria. Data from in vitro, in vivo, and clinical research were synthesized into three themes: pharmacological rationale, therapeutic efficacy, and formulation strategies. Promising results have been reported in melasma, acne, psoriasis, alopecia, and wound healing, where topical metformin has been shown to modulate melanogenesis, accelerate wound closure, reduce inflammatory cytokines, enhance hair regrowth, and support scar-free repair. Diverse formulations, including hydrogels, ethosomes, lipid nanoparticles, and niosomes, have been designed to improve skin penetration, drug retention, and therapeutic benefit while limiting systemic exposure.

Keywords: metformin, topical, dermatology

Introduction

Metformin is widely recognized as a first drug of choice oral antidiabetic agent, primarily used in the management of type 2 diabetes mellitus. Yet, new research has demonstrated its potential outside glucose control, particularly in dermatological contexts. Recent evidence indicates that metformin may possess anti-aging properties, particularly affecting the skin, which represents one of the earliest and most apparent signs of aging (A. Badria & A. Elgazar, 2020; Barzilai et al., 2016). Despite growing interest, no recent narrative review has comprehensively synthesized both pharmacological mechanisms and formulation strategies of topical metformin. This article aims to bridge that gap.

Several molecular pathways have been implicated in the dermatological actions of metformin. These include the downregulation of nuclear factor kappa B (NF-κB) signaling, particularly the p65 subunit, which is closely associated with cellular inflammation and senescence (Y. Sun et al., 2015). Metformin influences cellular metabolism by stimulating AMP-activated protein kinase (AMPK), a key regulator of energy balance that is essential for maintaining and repairing skin tissue. (Foretz et al., 2014; Lin et al., 2023). Furthermore, it has been reported to suppress the release of pro-inflammatory cytokines induced by ultraviolet B (UVB) radiation one of the key environmental contributors to photoaging and skin damage (Xiao et al., 2021). Metformin demonstrates strong anti-aging and anti-inflammatory potential for the skin in in vitro and animal studies, acting through antioxidant, anti-senescence, and regenerative mechanisms (Chen et al., 2022; Le Pelletier et al., 2021; Zhang, Qin, et al., 2024). Preliminary studies also indicate that metformin exhibits promising properties that may be harnessed for dermatological therapy including the enhancement of skin barrier function, restoration of normal cell turnover, protection against oxidative damage, and improved healing in wounded tissue (Chang & Choi, 2020; Xiong et al., 2022; Zhang, Shimozaki, et al., 2024).

Given its multifaceted pharmacological properties, topical metformin is not yet a mainstream dermatological therapy, it is under active investigation for conditions such as acne vulgaris, psoriasis, photoaging, and diabetic wounds. Early results point to its multifaceted actions anti-inflammatory, antioxidant, and regenerative which make it particularly attractive for chronic and hard-to-treat skin diseases (Afshar et al., 2024; EL-Komy et al., 2024; Monte-Serrano et al., 2022). Topical delivery of metformin offers the advantage of localized action with minimal systemic exposure, making it an attractive candidate for further formulation and clinical development. The objective of this review is to critically examine the current literature on the effectiveness of topical metformin in various skin disorders, as well as to explore the formulation strategies used to optimize its topical delivery and therapeutic potential.

Methodology

A narrative review was conducted to explore the current state of knowledge regarding the effectiveness and formulation strategies of topical metformin in dermatological applications. The methodology used in this study follows a thematic, literature-based approach rather than a formal systematic review protocol. Relevant literature was identified through an extensive search of scientific databases, including PubMed, ScienceDirect, Scopus, and Google Scholar, using combinations of the following keywords: “topical metformin,” “metformin dermatology,” “metformin skin formulation,” “metformin acne,” and “metformin wound healing.” Articles published in English between 2015 and 2025 were considered for inclusion. The inclusion criteria comprised original articles, randomized controlled trials (RCTs), clinical trials, preclinical studies (in vitro and in vivo), and case studies that specifically evaluated metformin in topical preparations or its dermatological effects. In contrast, studies focusing exclusively on oral metformin, polycystic ovary syndrome (PCOS), or non-dermatological diseases were excluded. Articles were

selected according to their relevance to the objectives of this review, including studies on the pharmacological rationale, mechanisms of action, formulation techniques, clinical or preclinical outcomes, and safety profiles of topical metformin. The selected publications were then analyzed qualitatively and organized into thematic sections, namely: (1) the pharmacological basis for the topical use of metformin, (2) evidence of efficacy in dermatological conditions, and (3) formulation strategies and challenges, allowing current evidence to be synthesized and gaps in knowledge to be highlighted for future research.

More specific keyword combinations were used to refine and expand the database search for each dermatological indication. For acne vulgaris, the following search string was applied: ("Acne Vulgaris"[Mesh] OR "acne"[tiab] OR "acne vulgaris"[tiab] OR pimples[tiab] OR "inflammatory acne"[tiab]) AND ("Metformin"[Mesh] OR "metformin"[tiab] OR "topical metformin"[tiab] OR "metformin gel"[tiab] OR "metformin cream"[tiab] OR "metformin ointment"[tiab]), yielding 10 records, of which only 1 study met the predefined inclusion and exclusion criteria after screening. For melasma, the search strategy was: ("Melasma"[Mesh] OR melasma[tiab] OR chloasma[tiab] OR "facial hyperpigmentation"[tiab]) AND (("Metformin"[Mesh] AND "Administration, Topical"[Mesh]) OR metformin[tiab] OR "topical metformin"[tiab] OR "metformin gel"[tiab] OR "metformin cream"[tiab] OR "metformin ointment"[tiab]), identifying 7 articles, of which 5 were eligible. The search for topical metformin in wound healing identified 27 records, with 13 studies fulfilling the inclusion and exclusion criteria, while evidence for topical metformin in alopecia and psoriasis was limited to 1 eligible article for each condition.

Result and Discussion

Topical Metformin in Melasma

Melasma is a common hyperpigmentation disorder, predominantly affecting women. It typically presents as symmetrical brownish patches on the face, ranging from light to dark brown, and is often exacerbated by prolonged exposure to sunlight. Several factors have been associated with the development of melasma, including genetic predisposition and gene polymorphisms, ultraviolet (UV) radiation, hormonal fluctuations, thyroid dysfunction, pregnancy, and drug-induced melasma, all of which contribute significantly to its pathogenesis (Ghasemiyeh et al., 2024). Both systemic and topical pharmacological agents are available for the treatment of melasma. The combination of hydroquinone, tretinoin, and a topical corticosteroid (commonly known as Kligman's formula) is considered the gold standard therapy. Other topical agents such as azelaic acid, kojic acid, ascorbic acid, cysteamine, metimazole, tranexamic acid, glutathione, and iron oxide-based sunscreens have also been used as alternatives or adjuncts (Doolan & Gupta, 2021).

A systematic review and meta-analysis comprising three randomized controlled trials (RCTs) involving a total of 140 patients with melasma demonstrated the potential of topical metformin. Treatment with 15% topical metformin resulted in a statistically significant decrease in Melasma Area Severity Index (MASI) scores relative to placebo after 56 days (mean difference [MD] = -0.56; 95% CI, -1.07 to -0.04; p = 0.034). Furthermore, topical metformin 30% exhibited comparable efficacy to Kligman's formula (hydroquinone 2%, tretinoin 0.025%, and

fluocinolone acetonide 0.01%) in ameliorating MASI scores after 56 days (MD = 0.19; 95% CI, -0.25 to 0.63; p = 0.390), suggesting its potential as an alternative to standard therapy (Mongkhon et al., 2023).

Another study comparing the efficacy of 30% metformin cream and 4% hydroquinone cream in patients with melasma showed that metformin resulted in a greater reduction in MASI score than hydroquinone, although the difference was not showing statistical significance (p = 0.054). While the improvement did not reach statistical significance, it approached the threshold, and metformin demonstrated a more favorable safety profile with fewer and milder adverse effects (Hussain et al., 2024). In a split-face interventional trial with 30 female participants diagnosed with melasma, the right facial side received microneedling plus topical metformin, whereas the left side was treated with microneedling in combination with a topical vitamin C solution. After intervention, hemi-MASI scores were significantly lowered in both groups (p < 0.001). The metformin group demonstrated a 48.29% improvement in hemi-MASI, whereas the vitamin C group showed a 37.19% improvement. Dermoscopic evaluation revealed markedly greater improvement in the microneedling plus metformin group than in the vitamin C group. These results suggest that microneedling with topical metformin is an effective and well-tolerated treatment option for melasma (Mahmoud et al., 2024). Another clinical split-face investigation was carried out in 18 melasma patients, where the right facial side was treated with microneedling plus topical metformin and the left side with microneedling and placebo. Treatments were administered four times at two-week intervals. The results, assessed using the hemi-mMASI score, demonstrated a significantly greater reduction on the metformin-treated side (2.39 ± 1.42) compared to the placebo-treated side (4.72 ± 1.27), with a statistically significant p-value of 0.001. The study concluded that topical metformin is more effective when combined with microneedling and does not produce noticeable side effects (Bessar et al., 2024).

Table 1. Summary of Clinical Studies on Topical Metformin for the Treatment of Melasma

Title & Author	Study design	Sample type	Intervention	Main outcome
Efficacy and safety of a novel weekly topical metformin-loaded peel-off mask in the treatment of melasma: a split-face, placebo-controlled study (EL-Komy et al., 2024)	Randomized controlled trial, split-face, placebo-controlled	Humans; 20 adult female patients with melasma	Topical 30% metformin peel-off mask applied once weekly for 12 weeks, compared with a placebo mask on the contralateral side of the face	Change in hemi-Melasma Area Severity Index (hemi-MASI) score
Combined micro-needling with topical metformin versus micro-needling with topical placebo in the treatment of melasma: a concurrent split-face study (Bessar et al., 2024)	Randomized controlled trial, concurrent split-face study	Humans; 18 patients with melasma	Micro-needling combined with topical metformin on one side of the face, compared with micro-needling with topical placebo on the other side (4 sessions, 2-week	Change in hemi-mMASI) score

			intervals)	
Topical metformin in the treatment of melasma: A preliminary clinical trial Banavase Channakeshavaiah R; Andanooru Chandrappa NK (Banavase Channakeshavaiah & Andanooru Chandrappa, 2020)	Randomized controlled trial; comparative study	Humans; 40 adult patients with melasma	Topical 30% metformin lotion compared with triple combination cream (hydroquinone 2% + tretinoin 0.025% + fluocinolone acetonide 0.01%) for 8 weeks	Change MASI score, global improvement scale, and patient satisfaction
Safety and efficacy of topical metformin 30% cream versus triple combination cream (Kligman's formula) in treating melasma: A randomized controlled study (AboAlsoud et al., 2022)	Randomized controlled trial in humans	40 patients with melasma, divided into 2 groups	Group 1: topical 30% metformin cream; Group 2: triple combination cream (Kligman's formula), for 8 weeks	Both groups showed significant and comparable reductions in MASI score; no significant difference between metformin and TCC in melasma reduction ($p = 0.968$)
Microneedling assisted delivery of metformin versus tranexamic acid in treating melasma: a randomized controlled study (Mohammady et al., 2025)	Randomized, prospective, parallel-group clinical trial	45 women with facial melasma, divided into 3 groups	Group A: microneedling + topical 15% metformin; Group B: microneedling + topical tranexamic acid (TXA) 50 mg/mL; Group C: topical modified Kligman's formula without microneedling, for 8 weeks	All groups showed significant reductions in mMASI; the greatest reduction occurred in the TXA group (45.28%), followed by Kligman (38.21%) and metformin (22.11%), with a significant difference ($p < 0.001$); patient satisfaction was highest in the TXA group, with minimal side effects in all groups

The anti-melanogenic effect of topical metformin in vivo is mediated through reduced expression of Microphthalmia-associated Transcription Factor (MITF), tyrosinase, and dopachrome tautomerase (DCT), all of which play essential roles in melanin synthesis. MITF serves as the central transcription factor controlling the expression of melanogenic enzymes, including tyrosinase, TRP1, and DCT, which are essential for melanin biosynthesis. The transcription of MITF is regulated by its promoter, which is activated through cyclic AMP response element-binding protein (CREB). Metformin inhibits the transcriptional activation of MITF by suppressing

CREB phosphorylation, a critical step in the cAMP signaling pathway (Lehraiki et al., 2014). In vivo studies on melanoma cells have further shown that metformin significantly inhibits both melanin production and release, in a dose- and time-dependent manner. Higher concentrations and longer exposure to metformin result in a greater depigmenting effect. Importantly, this occurs without cytotoxic effects on normal human melanocytes (NHM), demonstrating that metformin is a safe and potentially effective depigmenting agent for topical use in hyperpigmentation disorders such as melasma (Lehraiki et al., 2014).

Topical Metformin in Wound Healing

The application of topical metformin in Wistar Hannover rat full-thickness wound models, comprising diabetic and non-diabetic controls, resulted in a significant enhancement in the rate of wound healing compared with control groups. The expression levels of collagen type I and III were markedly increased on days 7 and 14 post-injury compared to baseline. Notably, wounds in diabetic rats treated with topical metformin exhibited healing rates comparable to those observed in non-diabetic rats. This finding indicates that metformin enhances the expression of COL1A1 and COL3A1, the genes encoding collagen types I and III, respectively. Type III collagen predominates during the proliferative phase, while type I collagen becomes more prominent during the remodeling phase, contributing to increased tensile strength of the wound tissue. In this study, metformin also reduced apoptosis by inhibiting the expression of p53 and c-Jun, two key transcription factors involved in oxidative stress-induced cell death. By downregulating these genes, metformin preserved vital cell populations critical to tissue regeneration. Additionally, the study showed that metformin reduced the expression of matrix metalloproteinases MMP-2 and MMP-9, enzymes responsible for collagen and extracellular matrix degradation, thus preventing excessive tissue breakdown. Furthermore, metformin significantly enhanced fibroblast proliferation and keratinocyte migration, two essential cellular processes in wound regeneration, leading to accelerated wound closure between 7 and 14 days post-treatment (Tombulturk et al., 2024).

An in vivo study on Sprague-Dawley rats with 2 cm Achilles tendon wounds compared the effects of a 6% metformin lotion to a placebo lotion. Results showed that topical metformin significantly promoted wound healing and reduced scar formation. The underlying mechanisms included: Anti-inflammatory effects through inhibition of HMGB1 and interleukin-1β (IL-1β); Antifibrotic action via suppression of transforming growth factor-beta 1 (TGF-β1) and alpha-smooth muscle actin (α-SMA); Enhanced skin regeneration by upregulating collagen I and downregulating collagen III; Activation of AMP-activated protein kinase (AMPK), a key regulator of inflammation and tissue remodeling. These results suggest that a 6% topical metformin lotion may serve as a novel therapeutic agent for promoting scar-free wound healing. One of the major advantages of topical metformin is its potent antifibrotic efficacy without the systemic side effects often associated with oral metformin therapy (Zhang, Shimozaki, et al., 2024).

Table 2. Summary of Preclinical Studies on Topical Metformin for Wound Healing

Title & Author	Study design	Sample type	Intervention	Main outcome
Microenvironment responsive nanocomposite hydrogel with NIR	In vivo	Diabetic SD rats	Metformin-laden CuPDA NPs composite hydrogel (Met@CuPDA	Antibacterial activity >95%; increased vascularization; reduced

Title & Author	Study design	Sample type	Intervention	Main outcome
photothermal therapy, vascularization and anti-inflammation for diabetic infected wound healing ((Zhu et al., 2023)			NPs/HG) plus NIR photothermal therapy	inflammation; accelerated wound healing
Topical application of metformin accelerates cutaneous wound healing in streptozotocin-induced diabetic rats (Tombulturk et al., 2022)	In vivo	Wistar albino rats (STZ-induced diabetes)	Topical metformin vs saline	Topical metformin reduced NF-κB p65 and MMP2/9 activity and accelerated wound healing in diabetic rats.
Metformin hydrochloride and wound healing: from nanoformulation to pharmacological evaluation (El-Ridy et al., 2019)	In vivo	Rats (Wistar); diabetic rats (experimental diabetes)	Metformin HCl niosomal gel (transdermal formulation) compared with oral metformin; prepared using various surfactants (Span 60, Span 40, Tween 80, cholesterol)	Entrapment efficiency 13–32%; vesicle size in the nano range; biphasic in vitro release; improved sustained antidiabetic effect vs oral doses; enhanced wound healing in diabetic rats receiving metformin formulations vs untreated controls.
Topical metformin accelerates wound healing by promoting collagen synthesis and inhibiting apoptosis in a diabetic wound model (Tombulturk et al., 2024)	In vivo	Wistar Hannover rats; STZ-induced diabetes	Topical metformin 3 mM vs saline	Metformin increased cell proliferation and collagen I/III, decreased p53/c-jun and apoptosis, and accelerated healing, including in diabetic wounds.
Pharmaceutical, clinical, and immunohistochemical studies of metformin hydrochloride topical hydrogel for wound healing application (Tawfeek et al., 2020)	In vivo + clinical study	Rats; humans with traumatic wounds and cutaneous ulcers	Topical MET-HCL hydrogel	Increased wound contraction from day 7; complete healing (21–30 days); increased TGF-β1; re-epithelialization and matrix repair.
Metformin lotion promotes scarless skin tissue formation through AMPK activation, TGF-β1	In vivo	Three-month-old female Sprague–Dawley	Topical application of 6% metformin lotion vs 0% lotion for 10 days (50 mg per paw per day)	Metformin lotion decreased HMGB1 and IL-1β, inhibited HMGB1 release, increased AMPK,

Title & Author	Study design	Sample type	Intervention	Main outcome
inhibition, and reduced myofibroblast numbers (Zhang et al., 2024)		rats, ~200 g, 2 cm skin incision wound model over the Achilles tendon		reduced TGF-β1, decreased myofibroblasts (α-SMA+), reduced collagen III, increased collagen I, and decreased scar formation.
Wound microenvironment self-adaptive all-in-one hydrogel for rapid healing of the diabetic wound (Li et al., 2024)	In vivo	Diabetic mouse model of diabetic wounds	Self-adaptive hydrogel based on PBA-modified gelatin + PVA (borate ester crosslinking) and liposomes containing metformin + L-arginine + L(+)-ascorbic acid, termed hydrogel@lipo composite	Reduced oxidative stress; increased angiogenesis; reduced inflammation; improved diabetic wound microenvironment; accelerated wound healing (healing within 2 weeks). Wound-Healing.docx
Anti-aging pharmacology in cutaneous wound healing: effects of metformin, resveratrol, and rapamycin by local application (Zhao et al., 2017)	In vivo	12-week-old female C57BL/6 mice; 12-week-old and 18-month-old female Sprague–Dawley rats; 6-month-old female New Zealand White rabbits; all used as full-thickness skin wound models	Daily topical application of metformin (MET) 2 μM, resveratrol (RSV) 50 μM, rapamycin (RAPA) 200 nM, or vehicle (ethanol) as control; 100–225 μL depending on wound size	MET and RSV, but not RAPA, improved wound healing in young rodents; MET showed more profound effects and exerted prominent regenerative effects in aged skin. Wound-Healing.docx
Metformin-loaded ethosomes with promoted anti-proliferative activity in melanoma cell line B16, and wound healing aptitude: Development, characterization and in vivo evaluation	In vitro and in vivo	B16 melanoma cells and a mouse wound healing model	Metformin-loaded ethosomes formulated with various ethanol concentrations; optimized ethosomal formulation incorporated into 5% carbomer gel;	Entrapment efficiency 13–32%; vesicle size in the nano range; increased permeation (85.8 ± 3.7); lower IC_{50} vs metformin solution (56.45 ± 1.47 vs 887.3 ± 23.2);

Title & Author	Study design	Sample type	Intervention	Main outcome
(Magdy et al., 2022)			compared with metformin solution and marketed Mebo® ointment	wound healing in mice 80.5 ± 1.9%, superior to Mebo® (56 ± 1%) ($p < 0.05$); increased growth factors IGF-1, FGF-1, PDGF-B, TGF-β. Wound-Healing.docx
Metformin induces the M2 macrophage polarization to accelerate the wound healing via regulating AMPK/mTOR/NLRP 3 inflammasome signaling pathway (Qing et al., 2019)	In vivo and in vitro	Sprague–Dawley rats; LPS-stimulated RAW264.7 macrophage cultures	Topical metformin 2 mM on rat wounds; mTOR activator (MHY1485) in the in vitro study	In vivo: faster wound healing; increased angiogenesis (CD31↑); increased M2 and decreased M1 macrophages; IL-10↑ and IL-1β↓; decreased NLRP3 inflammasome activation. In vitro: metformin promoted M1→M2 polarization, increased AMPK activation, decreased mTOR activation, reduced NLRP3 inflammasome activation, increased IL-10 and decreased IL-1β, and increased VEGF. Wound-Healing.docx
Metformin as a Modulator of Autophagy and Hypoxia Responses in the Enhancement of Wound Healing in Diabetic Rats (Tombulturk et al., 2025)	In vivo and in vitro	STZ-induced diabetic Wistar Hannover rats; HaCaT cells and fibroblasts under hypoxic conditions	Topical metformin 3 mM applied to wounds for 14 days; 1% O_2 hypoxia treatment in cells	Increased expression of LC3B and Beclin-1 (autophagy markers); increased total AMPK (tAMPK); decreased HIF-1α under hypoxia; enhanced wound closure and tissue regeneration. Wound-Healing.docx
In Vitro and In Vivo Evaluation of Metformin Hydrochloride Hydrogels Developed with Experimental Design in the Treatment of Burns (Ozyilmaz et al., 2023)	In vivo and in vitro	Wistar rats, burn wound model; 2 groups, 7 rats each	In situ hydrogels containing metformin HCl (Poloxamer 407®, Carbopol 934®, Na-CMC); metformin concentrations 4 mg/g, 6 mg/g, 8 mg/g; two optimal formulations (4 mg/g and 8 mg/g)	Significantly reduced burn wound size after 29 days; effectiveness depended on gelling agent type and metformin concentration; metformin-poloxamer hydrogels were the most effective. Wound-Healing.docx

Title & Author	Study design	Sample type	Intervention	Main outcome
			tested in vivo	
Rational design of flexible microneedles coupled with CaO_2@PDA-loaded nanofiber films for skin wound healing on diabetic rats (Zeng et al., 2022)	In vivo	Diabetic rats	Flexible microneedle dressing loaded with metformin plus a backing nanofiber patch containing CaO_2@polydopamine nanoparticles	Increased angiogenesis (CD31↑); reduced TNF-α (decreased inflammation); antibacterial activity against S. aureus and E. coli; accelerated healing of diabetic wounds. Wound-Healing.docx

Further evidence from preclinical and clinical trials using metformin hydrochloride gel in both animal models and human subjects supports its wound-healing potential. In rodent models, wounds treated with metformin gel showed significantly faster healing as early as day 7 compared to those treated with non-medicated gel. In clinical settings, traumatic wounds achieved complete closure within 21 days, and skin ulcers healed entirely within 30 days of treatment. Histopathological analysis revealed complete recovery of connective tissue and re-epithelialization, indicating full skin regeneration. Immunohistochemical findings showed increased expression of TGF-β1, a critical growth factor in tissue repair and regeneration (Tawfeek et al., 2020).

Topical metformin and skin regeneration

Research on topical metformin for skin regeneration highlights several promising findings focusing on its ability to enhance skin repair, proliferation of stem cells, and reduction of scar tissue formation. In a rat-based model of dermal wound healing, a novel topical metformin lotion (6%) inhibited scar tissue formation. Metformin activated AMPK, inhibited TGF-β1 (a pro-fibrotic factor), decreased myofibroblast numbers, and altered collagen composition favoring collagen I over collagen III. These effects promote high-quality, scarless skin regeneration during wound healing (Zhang, Shimozaki, et al., 2024). Metformin's regenerative potential may be associated with its anti-inflammatory, anti-fibrotic, and stem cell proliferative effects. It improves angiogenesis (new blood vessel formation), collagen synthesis, and skin thickness, all key to skin repair (Ebrahimnejad et al., 2023).

In a skin expansion model study, 20 male rats were used and divided into two groups: 10 rats received topical metformin, while the other 10 received a placebo. Skin stretching was performed using silicone expanders that were gradually inflated with fluid. Several analyses were conducted, including skin thickness measurement, collagen density, angiogenesis (new blood vessel formation), skin stem cell activity, as well as microscopic and molecular evaluations (immunohistochemistry, immunofluorescence, and western blot). The results demonstrated that topical metformin considerably elevated both epidermal and dermal thickness compared to the control set. The metformin-treated set showed an enhancement in collagen I and III deposition, along with more organized collagen structures. There was also a greater number of actively dividing cells, as evidenced by positive staining for PCNA, Ki67, Aurora B, and pH3 markers. Additionally, angiogenesis was markedly enhanced in the metformin group, with a remarkably elevated in both microcirculation and vascular density in metformin-treated skin.

The metformin group also showed an increase in both the quantity and activity of Epidermal Stem Cells (ESCs) (CK14+/PCNA+) and Hair Follicle Bulge Stem Cells (HFBSCs) (CK15+/PCNA+). In conclusion, topical metformin enhances the regenerative capacity of mechanically expanded skin through: Increased proliferation of skin stem cells; Enhanced collagen synthesis; Improved vascularization. These findings suggest that topical metformin may serve as a non-invasive therapeutic alternative to accelerate skin regeneration in tissue expansion procedures or chronic wound management (Xiong et al., 2022).

Topical Metformin in Acne Treatment

Oral metformin has proven beneficial in treating acne vulgaris, particularly in individuals exhibiting insulin resistance or in those whose condition does not respond to standard therapeutic approaches. Metformin's therapeutic action in acne is mainly attributed to its ability to lower insulin-like growth factor-1 (IGF-1), suppress the mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway, exert anti-inflammatory effects, and regulate gut microbiota**.** Several studies have demonstrated that metformin has comparable efficacy to doxycycline**,** making it a viable alternative or adjunctive therapy to enhance the effectiveness of other acne treatments. Furthermore, metformin possesses a more favorable safety profile compared to isotretinoin, with milder and better-tolerated side effects (Szefler et al., 2024).

A clinical study involving 27 female patients with acne vulgaris investigated the effects of 30% topical metformin gel in comparison with placebo. Participants were instructed to apply the gels to each side of the face over a period of 12 weeks. The results showed a significant improvement in comedones, papules, and nodules, although there was no notable improvement in pustules. While the total number of lesions increased one month after cessation of therapy, the number of comedones and papules remained substantially lower in the metformin-treated group compared to placebo. Importantly, no adverse effects were reported during the study, highlighting the potential safety and tolerability of topical metformin in the management of acne (EL-Komy et al., 2023, 2024).

Topical Metformin in Alopecia Treatment

Topical metformin has shown effectiveness in managing Central Centrifugal Cicatricial Alopecia (CCCA). CCCA is an alopecia characterized by inflammatory scarring, predominantly affecting middle-aged Black women. The condition typically begins at the vertex of the scalp and progresses centrifugally. Patients may experience symptoms such as burning, pain, or pruritus, although some cases are asymptomatic. Standard treatment options include topical minoxidil, topical and intralesional corticosteroids, antifungal shampoos, and oral antibiotics. In a case series, three patients with CCCA who were unresponsive to standard therapies received topical metformin 10% as an adjunctive treatment. All three patients experienced significant greater hair density after 6 to 10 months of topical metformin therapy (Williams et al., 2025).

The use of topical metformin has proven beneficial in Alopecia Areata (AA), an autoimmune condition characterized by inflammation of hair follicles. Research findings suggest that its therapeutic effects are linked to anti-inflammatory and immunomodulatory actions, including inhibition of NF-κB signaling, suppression of effector T cell proliferation, reduction of pro-inflammatory cytokines, and modulation of cytokine receptor activity. Furthermore, metformin supports immune regulation through an increased proportion of Tregs. It has also been reported to activate autophagy increase the multiplication of hair follicle stem cells, both crucial

for follicular regeneration. These mechanisms are consistent with experimental evidence of metformin-induced hair growth in vitro and in vivo studies of cicatricial alopecia (Kokhabi et al., 2023).

A case report described two patients who exhibited clinically apparent hair regrowth following the application of topical 10% metformin formulated in Lipoderm™, a transdermal cream designed to optimize skin absorption. Neither patient experienced telogen effluvium prior to regrowth. Notably, neither was on oral metformin, and no systemic adverse effects were reported. Both patients only experienced mild scalp dryness and irritation, which resolved with the use of topical moisturizers or emollients. The 10% concentration was chosen based on pharmacists' recommendations to maximize local therapeutic effects while minimizing systemic absorption. Dose escalation may be considered in patients who respond well and tolerate topical metformin (Araoye et al., 2020).

An experimental investigation assessed the impact of metformin on hair follicle neogenesis using a murine model of follicle reconstitution, which employed three-dimensional aggregates of self-organized epidermal and dermal cells cultured in vitro. Metformin induced a direct stimulation of alkaline phosphatase (ALP) activity and upregulated both protein and mRNA expression of critical molecular markers, including HGF, CD133, ALP, β-catenin, and SOX2, thereby enhancing the persistence of reconstructed hair follicle structures. These results indicate that metformin may facilitate hair follicle restoration in vitro through the enhancement of dermal cell inductive potential, supporting its further evaluation for clinical application in the management of androgenetic alopecia in both sexes (C. Sun et al., 2021).

Topical metformin in Psoriasis

A meta-analysis comprising three randomized controlled trials (RCTs) and 148 patients with psoriasis demonstrated that oral dosing of metformin significantly improved treatment efficacy, as demonstrated by a 75% diminution in the Psoriasis Area Severity Index (PASI) and a 75% diminution in the Emergency Severity Index (ESI). Metformin demonstrated a markedly greater improvement in metabolic syndrome parameters relative to placebo in patients with psoriasis (Huang et al., 2023). Another study reported a marked decrease in PASI scores among psoriasis patients with concomitant metabolic syndrome after metformin treatment (Stanescu et al., 2021).

An in vivo study in mice with imiquimod 5%-induced psoriasis demonstrated that topical metformin gel (10% and 15%) significantly reduced erythema and scaling scores compared with the imiquimod-only group. The effect of 15% metformin was stronger than that of 10% and approached the efficacy of clobetasol, a potent topical corticosteroid. Imiquimod increased IL-17 and IL-23 levels, two key cytokines in psoriasis pathogenesis. Treatment with 10% and 15% metformin gel significantly reduced IL-17 and IL-23 levels compared with the imiquimod-only group. Topical metformin also improved skin structure by reducing epidermal thickening, decreasing inflammatory cell infiltration, and eliminating rete ridges (epidermal pathological protrusions) (Al-Saedi et al., 2019).

Table 2. Summary of Studies on Topical Metformin for Acne, Alopecia, and Psoriasis

Title	Study design	sample type	Intervention	Main outcome
Topical metformin	Randomized controlled	Humans; 27 female	Topical 30% metformin gel applied	Change in the number of acne

30% gel in the treatment of acne vulgaris in women, a split face, placebo-controlled study (EL-Komy et al., 2023)	trial, split-face, placebo-controlled	patients with acne vulgaris	to one side of the face and placebo to the other side for 12 weeks	vulgaris lesions (comedones, papules, nodules, pustules) from baseline to the end of therapy and 4 weeks after therapy.
Adjuvant use of topical metformin with standard therapies in recalcitrant central centrifugal cicatricial alopecia: A case series (Williams et al., 2025)	Case series	3 Black women with CCCA resistant to standard therapy	Addition of 10% topical metformin cream (in case 1 combined with 5% minoxidil; in cases 2 and 3 together with high-dose topical minoxidil, topical/intralesional steroids, doxycycline) as an adjuvant to standard regimens, used nightly for about 10 months	All three cases showed marked improvement in hair density and regrowth after adding topical metformin, after previously showing only minimal improvement with standard therapy alone.
Effect of metformin gel against imiquimod induced psoriasis in mice (Al-Saedi et al., 2019)	In vivo	Adult Swiss albino mice, divided into 5 groups (Vaseline control, imiquimod only, imiquimod + clobetasol, imiquimod + 10% metformin gel, imiquimod + 15% metformin gel)	Psoriasis induced by 5% imiquimod cream on the backs of mice for 6 days; treatment groups additionally received topical clobetasol or 10% or 15% metformin gel over the same period	Imiquimod increased erythema and scaling scores and skin tissue IL-17 and IL-23 levels; 10% metformin gel significantly reduced IL-17 and IL-23 compared with the induction group, while 15% metformin produced greater cytokine reduction and improved epidermal thickening and inflammatory infiltration on histopathology.

Adverse Effects of Topical Metformin

Most human clinical studies included in systematic reviews reported no serious adverse events related to topical metformin use. In dermatological studies on melasma, acne, wound healing, and hair growth, topical metformin was documented as safe and generally well tolerated. A few cases of mild local irritation, such as erythema, pruritus, and mild burning sensations, were rarely observed and generally resolved spontaneously without intervention. This suggests that topical metformin has an excellent safety profile, with fewer side effects compared to

standard therapies such as hydroquinone for melasma or retinoids/other topical agents for acne (Afshar et al., 2024).

Formulation of Topical Metformin

Topical metformin can be prepared in ointment form. A simple ointment based on the British Pharmacopoeia (BP) is prepared by melting 4.75 g of hard paraffin at 60 °C, followed by the addition of 4.75 g of wool fat and 4.75 g of cetostearyl alcohol. The mixture is stirred and allowed to cool at room temperature. Subsequently, 1.0 g of metformin HCl, thymol oil at varying concentrations, and 78.75 g of white soft paraffin are incorporated. The prepared ointment was then subjected to physicochemical characterization, showing favorable properties. A metformin HCl ointment with high in vitro release was successfully developed, and drug penetration through artificial membranes was enhanced by thymol oil, particularly at higher concentrations, via the transdermal route (Khan et al., 2020) .

Topical metformin has also been formulated in various hydrogel bases. Drug content, spreadability, homogeneity, viscosity, and pH were examined in the gel formulations. In vitro release studies showed that metformin hydrogels exhibited high drug content, good homogeneity, easy spreadability, and non-irritant properties. Metformin hydrogels also demonstrated optimal viscosity and shear stress. Carbopol was identified as the most suitable gel base, yielding the highest metformin release (Tawfeek et al., 2020).

Formulations of topical metformin utilizing ethosomes have been created to facilitate greater skin absorption and exert antitumor properties against experimentally developed skin cancer in rat models. Ethosomes are flexible lipid nanovesicles composed of phospholipids, ethanol, and occasionally isopropyl alcohol and cholesterol. They enhance drug penetration into deeper skin layers. Using a Box–Behnken experimental design with three key variables lecithin (lipid bilayer former), cholesterol (stability enhancer), and ethanol + isopropyl alcohol (skin penetration enhancers)—the optimized formulation contained 2.08% lecithin, 0.52% cholesterol, and 37.5% ethanol. This formulation achieved an entrapment efficiency (EE%) of 98.4%, vesicle size of 124 nm, zeta potential of −60.08 mV (stable), 55.04% drug release after 8 hours, and 97.6% skin permeability. Transmission electron microscopy (TEM) revealed spherical, homogeneous vesicles without aggregation. Differential scanning calorimetry (DSC) confirmed the successful encapsulation of metformin in ethosomes. Skin permeation studies showed superior drug release and penetration compared with other formulations. In vivo testing in rats with DMBA-induced skin cancer demonstrated significant tumor lesion reduction, histological skin improvement, and no major hepatic or renal toxicity, with normal biochemical parameters. These results indicate that ethosomal metformin gel is highly effective in skin penetration, drug retention, and antitumor activity, with minimal systemic side effects (Mousa et al., 2022).

Solid lipid nanoparticle-based nanogels of metformin have also been developed, demonstrating stability, effective particle size control, enhanced skin penetration, and favorable chemical safety. The inclusion of Span®60 as a co-emulsifier reduced particle size. All Tween–Span combinations yielded small particle sizes with low polydispersity index (PDI), indicating uniformity, and high zeta potential, confirming good stability. Ex vivo studies showed higher metformin deposition in skin layers and receptor compartments for nanogels compared with conventional gels, indicating superior skin penetration and potential for clinical translation (Rostamkalaei et al., 2019).

Additionally, transdermal niosomal metformin gels have been formulated. These offer several advantages, including improved and sustained glycemic control, accelerated diabetic wound healing, and potential as alternative topical therapy for diabetes. Niosomes were prepared using the Thin Film Hydration method with Span 60, Span 40, Tween 80, and cholesterol in varying ratios. Entrapment efficiency ranged from 13% to 32%, with vesicle sizes in the nanometer range. In vitro drug release exhibited a biphasic pattern, indicating sustained release. In vivo studies in rat model of diabetes demonstrated that niosomal metformin hydrochloride topical gel administered every 48 hours provided more prolonged antidiabetic effects than daily oral metformin, and while also improving the rate of wound healing in contrast to untreated controls (El-Ridy et al., 2019).

Conclusion

Topical metformin emerges as a promising dermatologic therapy with multifaceted pharmacological actions, including anti-inflammatory, antioxidant, anti-fibrotic, and regenerative effects that are relevant across several skin disorders. Evidence from preclinical and clinical studies indicates beneficial outcomes in melasma, acne, psoriasis, alopecia, and particularly wound healing, where topical metformin modulates key pathways such as AMPK, NF-κB, melanogenesis regulators, and profibrotic signaling, leading to improved pigmentation control, accelerated re-epithelialization, enhanced collagen remodeling, and reduced scar formation. Advances in formulation science such as hydrogels, peel-off masks, microneedle systems, ethosomes, lipid nanoparticles, and other nanocarriers have significantly improved cutaneous delivery, local retention, and therapeutic efficacy while minimizing systemic exposure and local irritation.

Declaration of Competing Interest

The author declares that they have no conflicts of interest in relation to this manuscript. The study was conducted in an independent manner, without monetary support, sponsorship, or engagement from pharmaceutical firms or commercial parties that could potentially introduce bias.

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