"MORTAR & PENCIL" CONCORDIA UNIVERSITY WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Topical Metformin: A Review of Clinical Evidence and Compounding Considerations

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Abstract

Background: Metformin is widely used for type 2 diabetes mellitus, but emerging evidence highlights its anti-inflammatory, antifibrotic, and wound-modulating effects via activation of AMP-activated protein kinase (AMPK). These properties have spurred interest in topical metformin for dermatologic and tissue-healing applications, despite the lack of FDA-approved formulations. This literature review evaluates the safety, efficacy, and compounding considerations of compounded topical metformin, providing rationale and proposed mechanisms for topical use while summarizing preclinical and clinical evidence.

Methods: A comprehensive search of PubMed, EBSCO, Medline, and International Pharmaceutical Abstracts identified English-language studies (January 1, 2019-October 1, 2025) involving topical or locally applied metformin in human or animal models. Exclusions included oral-only metformin studies and systematic reviews. Additional guidance was gathered from United States Pharmacopeia <795> standards, Centers for Disease Control and Prevention or Food and Drug Administration publications, Trissel's Stability of Compounded Formulations, and the International Journal of Pharmaceutical Compounding.

Results: Across 12 studies, topical metformin (concentrations 0.5% to 30%) consistently improved inflammation, pigmentation, scar characteristics, periodontal outcomes, and hair growth, with minimal adverse effects. Evidence is strongest for chronic periodontitis and melasma, with promising early findings in wound healing and central centrifugal cicatricial alopecia. Limitations include small sample sizes, heterogeneous formulations, and lack of pharmacokinetic data.

Conclusion: Topical metformin is a mechanistically rational compounded therapy showing promising therapeutic potential with broad dermatologic applicability. It appears well tolerated and can produce clinically meaningful improvements. Standardized formulations tested in large, multicenter randomized controlled trials are needed to support broad clinical adoption.

Metformin hydrochloride is one of the most widely used antihyperglycemic treatments for type 2 diabetes mellitus worldwide and is traditionally taken orally. Although it is not without risks, metformin has consistently shown a favorable safety profile. In diabetes, metformin works by enhancing insulin sensitivity and promoting glucose uptake in myocytes.[1] Metformin has also shown potential in activating AMP-activated protein kinase (AMPK) pathways, contributing to its insulin-sensitivity-promoting effects. AMPK pathway activation is associated with improved cellular energy balance, reduced oxidative stress, inflammation modulation, and enhanced wound repair.[2] These mechanistic properties have prompted growing interest in metformin's potential use as a topical therapy for dermatologic and wound-related conditions.

Topical metformin has been investigated for several dermatologic conditions that share underlying pathways of chronic inflammation, fibrosis, and impaired tissue repair. Recent studies have explored compounded topical metformin for conditions including chronic periodontitis, melasma, central centrifugal cicatricial alopecia (CCCA), and diabetic wound healing. Chronic periodontitis is an inflammatory disorder of the teeth-supporting structures that results in pocket formation and bone destruction. Melasma is an acquired condition characterized by hyperpigmented macules on the face resulting from dysregulated melanogenesis. Central centrifugal cicatricial alopecia is a type of scarring hair loss that leads to irreversible follicular destruction, typically focused on the crown of the scalp. Poorly healing diabetic wounds commonly arise from prolonged inflammation, oxidative stress, and impaired angiogenesis in the presence of poor healing conditions propagated by hyperglycemia. Topical administration offers an appealing route for medications intended to exert local effects while minimizing systemic exposure and gastrointestinal intolerance. However, the United States Food and Drug Administration (FDA) has not approved topical metformin for any indication, and much of the available evidence is early-stage, heterogeneous, and limited by small sample sizes. Multi-center clinical human trials and

evaluations of community compounding viability are limited.

This literature review summarizes current clinical and preclinical findings on compounded topical metformin, outlines safety and toxicology considerations, and discusses compounding principles relevant to certain dermatologic and wound-care practices such as chronic periodontitis, melasma, central centrifugal cicatricial alopecia, and diabetic wounds. The authors identify and discuss gaps in the research literature to guide future research and support evidence-based prescribing.

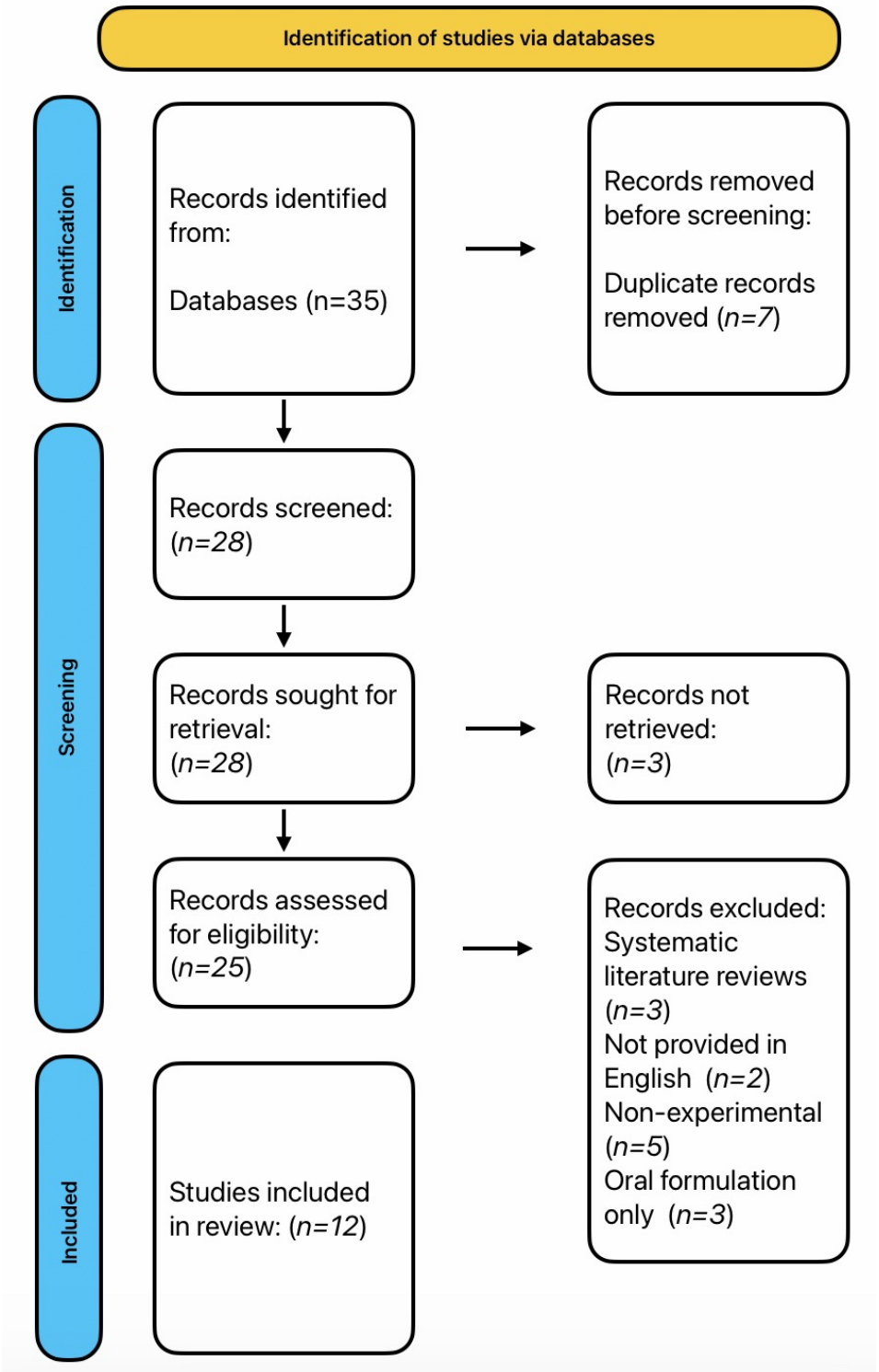
Materials & Methods

We conducted a comprehensive literature review to evaluate the safety and efficacy of compounded topical metformin. Eligible studies included animal or human data published between January 1, 2019, and October 1, 2025, written in English, and involving topical or locally applied metformin formulations. This timeframe was selected because compounded topical metformin formulations are an emerging area of interest, with most clinical studies, case reports, and practical compounding applications appearing in the literature after 2018. Exclusion criteria included studies evaluating only oral metformin and systematic reviews.

Databases searched included PubMed, EBSCO, Medline, and International Pharmaceutical Abstracts using the keyword phrase "compounded topical metformin." Additional guidance was gathered from United States Pharmacopeia (USP) <795> standards, Centers for Disease Control and Prevention or FDA publications, Trissel's Stability of Compounded Formulations, and the International Journal of Pharmaceutical Compounding.

We generated a PRISMA flow diagram and an overview of referenced studies to summarize the search process (Figure 1 and Table 1).

FIGURE 1. PRISMA Flow Diagram of the Study Selection Process.



Results

Chronic Periodontitis

Each chosen study evaluating topical metformin for chronic periodontitis included prior treatment with scaling and root planing (SRP), the standard first-line treatment, along with improved dental hygiene. After this initial evaluation and treatment, participants received a 1% to 1.5% metformin gel, chip, or biofilm applied to the treatment site, compared with placebo.

A randomized, placebo-controlled trial involving 15 men and 15 women involved placing 1.5% metformin gel at the site of SRP and placing an identical placebo gel in the control group.[3] Periodontal status was measured using numerous clinical and radiographical variables from baseline to 3 and 6 months, including plaque index (PI), sulcus bleeding index (SBI), probing pocket depth (PPD), and clinical attachment level (CAL). The authors found statistically

significant differences in each treatment measurement from baseline to 6 months and suggest that 1.5% metformin gel may be an SRP adjunctive treatment that improves long-term dental health. Another randomized placebo-controlled trial involved 25 patients and the placement of a biodegradable 1% metformin chip at the site of SRP compared to identical placement of a placebo chip in the control group.[4] The described metformin chip included a 1% metformin solution incorporated into a polyethylcellulose membrane developed by PerioBiologics LLP. Periodontal status was measured from baseline to 3 months using PI, PPD, CAL, modified sulcus bleeding index (mSBI), and a microbial load quantified by measuring *Porphyromonas gingivalis* CFUs. Statistically significant improvements were seen in PI, CAL, and P. gingivalis CFUs, and the authors again suggest that a 1% metformin product may be an effective SRP adjunctive treatment that improves long-term dental health. Another randomized placebo-controlled trial involving only eight patients assigned to four treatment groups compared placement of a 1% metformin biofilm with plasma rich in growth factor (PRGF) to PRGF only, 1% metformin only, and SRP only.[5] Periodontal status was measured from baseline to 3 and 6 months using gingival index, vertical probing depth, and vertical clinical attachment level measurements. Digital subtraction radiography was performed at baseline and at 6 months. These radiographic measurements showed a statistically significant improvement in the 1% metformin with PRGF biofilm group; however, clinical measurements did not reveal any treatment advantage.

Melasma

Each chosen study evaluating topical metformin for melasma compared it with a control group using common melasma treatments as well as placebo. Melasma is often treatment resistant and may require repeated use of agents with significant risk.

A randomized controlled trial involving 40 patients compared applying 30% metformin cream to the face once daily at night with a triple combination cream commonly referred to as Kligman's formula, which includes hydroquinone, tretinoin, and hydrocortisone, once daily.[6] Clinical outcome was measured from baseline to 8 weeks and included the melasma area severity index (MASI) score. No statistically significant difference was observed between the treatment groups, although both showed statistically significant and similar improvements in MASI. The authors also assessed adverse effects, and the metformin group reported fewer events. The authors suggest that a 30% metformin cream may be a more tolerable treatment option than the common Kligman's formula while also minimizing topical corticosteroid exposure.

TABLE 1. Overview of Referenced Studies

Article & Year	Topic	Study Type	Sample Size	Treatment Protocol	Follow-Up	Results
Patil et al. (2022)	Periodontitis	RCT	30	SRP + Placebo gel vs. SRP + Metformin 1.5% gel	3 & 6 month	Improved PI, PPD, SBI & CAL in metformin treatment group
Soundarya et al. (2025	Periodontitis	RCT	25	SRP + Placebo chip vs. SRP + Metformin 1& chip	3 month	Improved PI, PPD, CAL, mSBI & CFU in metformin treatment group
Shabnam et al. (2019)	Periodontitis	RCT	8	PRGF vs. PRGF + Metformin 1% biofilm vs. Metformin 1% biofilm vs. SRP	3 & 6 month	Improved radiographic measurements in metformin + PRGF group
Eldahshan et al. (2021)	Melasma	RCT	40	Metformin 30% cream vs. TCC (Kligman's)	8 week	Improved MASI & ADR in metformin treatment group
Shamma et al. (2024)	Melasma	RCT	20	Metformin 30% facemask vs. Placebo facemask	12 week	Improved hemi-MASI in metformin treatment group
Hussein et al. (2024)	Melasma	RCT	62	Metformin 30% cream vs. Hydroquinone 4% cream	12 week	Improvement in treatment goals met
Granja et al. (2024)	CCCA	Case report	1	Metformin 10% cream	6 month	Significant hair regrowth
Araoye et al. (2024)	CCCA	Case report	2	Metformin 10% cream	6 month	Significant hair regrowth
Bao et al. (2024)	CCCA	Case series	12	Metformin hydrochloride LD + adjuvant	N/A	Decreased scalp pain, pruritus & inflammation with hair regrowth
Tombulturk et al. (2023)	Wound/Scar	Animal	24	Saline vs. Metformin 3 mM sponge	14 day	Marker decrease in metformin treatment group
Elsayed et al. (2019)	Wound/Scar	Animal	30	Metformin niosomal 100mg/kg vs. Metformin oral	14 day	Inability to produce systemic effect
Hesami et al. (2022)	Wound/Scar	RCT	53	Placebo gel vs. Metformin 0.5% gel	3 month	Improvement in VSS in metformin treatment group

Abbreviations: ADR, adverse drug reaction; CAL, clinical attachment level; CFU, colony-forming units; LD, low-dose; MASI, melasma area and severity index; mSFI, modified sulcus fluid index; PI, plaque index; PPD, probing pocket depth; PRGF, platelet-rich growth factor; RCT, randomized controlled trial; SBI, sulcus bleeding index; SRP, scaling and root planing; TCC, triple combination cream; VSS, Vancouver scar scale

A randomized, placebo-controlled trial of 20 female patients involved placing a facemask with a split-face design: placebo on one half and a 30% metformin solution on the other. Clinical outcomes were measured from baseline to 12 weeks using a modified Hemi-MASI score that allows for split-face evaluation. Outcomes were reassessed at 12 weeks post-treatment, alongside tolerability assessments throughout the treatment course. The metformin group showed a statistically significant difference in Hemi-MASI score at 12 weeks, followed by a 12-week post-treatment assessment with no significant adverse events reported. The authors suggest this may be a unique therapeutic option given the minimal dosing (facemask applied only once weekly), tolerability, and proposed durability. Another randomized controlled trial including 62 patients compared a 30% metformin cream with a 4% hydroquinone cream.[8] Clinical outcome was measured from baseline to 12 weeks, and again 4 weeks post-treatment, utilizing the MASI score. Based on MASI measurements, the authors deemed 80.6% of metformin-treated patients to have met treatment goals, whereas only 58.1% in the hydroquinone group did; however, they found no statistically significant difference between treatment groups. Although tolerability profiles were similar across treatment groups, the authors concluded that 30% metformin cream may be a safer and more effective melasma treatment.

Central Centrifugal Cicatricial Alopecia

Central centrifugal cicatricial alopecia (CCCA) is a scarring hair loss condition that is often resistant to traditional treatment options. These studies evaluate metformin as a last-line option with potential but not guaranteed results.

One case report described the use of a 10% metformin cream in a single patient with recalcitrant CCCA.[9] This patient had severely advanced hair loss and was refractory to all prior treatment attempts. Significant hair regrowth was reported, and the author suggests that, based on other evaluated reports, topical metformin CCCA treatment deserves further investigation. Another case report described the use of a 10% metformin cream for recalcitrant CCCA, applied daily by two patients.[10] As before, both patients had advanced hair loss and were refractory to all prior first-line treatment attempts. Both patients reported significant hair regrowth, with minimal, if any, adverse or toxic events. In one case, metformin was used alone, and hair regrowth was seen in 6 months; in the other, metformin was used adjunctively, and benefits were reported after 4 months. A separate case series of 12 patients with treatment-refractory CCCA treated with low-dose oral metformin for diabetes found that nine patients experienced decreased scalp pain, pruritus, and inflammation, with six patients reporting increased hair growth. Evidence of CCCA-related gene expression modulation by metformin in this series also supports the direct application of topical metformin as a potential treatment modality for CCCA by minimizing inflammation.

Diabetic Wounds

In diabetic wounds, prolonged inflammation is associated with additional barriers to proper healing. Hyperglycemic conditions increase oxidative stress, resulting in fibroblast apoptosis and a weakened collagen response. Metformin is theorized

to mitigate this hyperglycemia-associated oxidative stress and delayed healing effects, with the potential to also provide anti-inflammatory benefits when applied locally to non-diabetic wounds.[11]

A full-thickness incisional wound animal trial involved 12 diabetic and 12 non-diabetic mice randomized to four groups receiving either topical metformin or topical saline treatment.[12] Metformin was applied to the wounds locally using a sterile 3 mM metformin sponge, although it is unclear whether the wound was packed. Percent wound closure utilizing a simple equation was measured from baseline to 14 days, as well as measurements for collagen I/III, p53, c-jun mRNA expression, and apoptosis via TUNEL assay. A statistically significant increase in wound closure and decrease in all inflammatory markers was seen in the diabetic metformin treatment group, with every marker except apoptosis seen in the non-diabetic metformin treatment group as well. A preclinical and pharmacological study successfully created a niosomal metformin gel demonstrating biphasic release properties.[13] This product was evaluated in a mouse study, which showed similar antidiabetic efficacy when compared to oral metformin. The mice were also intentionally wounded, and the niosomal metformin gel showed potential for significantly improved diabetic wound healing when applied locally, with an increase in relevant growth factors. Although the study used a gel preparation, the authors theorized the potential use of a metformin niosomal patch for local diabetic wound healing. A randomized blinded clinical trial involving 53 patients exhibiting hypertrophic or keloid scarring involved the comparison of a 0.5% metformin gel and a placebo gel applied twice daily.[14] Scar improvement was measured from baseline to 3 months using the Vancouver Scar Scale. The metformin group showed statistically significant improvements in scar height, vascularity, pliability, and pigmentation. No adverse events were reported with metformin, and the authors suggest it may benefit scar healing but recommend further evaluation of dosing and application criteria to develop a standard protocol.

Safety

Systemic metformin is associated with gastrointestinal intolerance and rare lactic acidosis. Topical administration largely avoids systemic absorption, and across all human studies reviewed, adverse effects were minimal and primarily limited to mild localized irritation. Dermal toxicology data suggest no significant systemic accumulation at compounding concentrations (0.5–30%), although long-term safety remains insufficiently characterized.

Compounding and Formulation Considerations

Throughout the evaluated studies, compounded vehicles included gels, creams, ointments, sponges, membranes, films, and niosomal carriers. Concentrations ranged from 0.5–5.0% for wound and scar applications, 1.0–1.5% for periodontal applications, and 10–30% for CCCA and melasma. Preliminary compounding research indicates metformin is stable in hydrophilic ointment bases and compatible with several semisolid vehicles.[15] Standard USP <795> principles apply and include assigning appropriate beyond-use dates, documenting excipient compatibility, considering pH and solubility, and selecting vehicles that promote adequate skin penetration without irritation.[16]

Given metformin's mechanistic role in inflammation and wound modulation, future compounded formulations, such as combinations with antimicrobials or growth-factor-modulating agents, warrant further evaluation.

Compounded topical metformin, used off-label for dermatological conditions, presents notable regulatory and ethical considerations. These formulations fall under FDA section 503A, which exempts them from full FDA approval and certain manufacturing requirements. Mandates do remain for patient-specific prescriptions, adherence to USP standards, and oversight by state boards to mitigate risks. Ethically, clinicians must prioritize informed consent, ensuring patients understand the absence of rigorous FDA efficacy and safety evaluations. This includes a recommendation to use compounded options only when FDA-approved alternatives are inadequate or unavailable.

Discussion

Although metformin shows potential as an effective topical treatment, evidence supporting topical metformin remains early and heterogeneous. Most human studies are small, short-term trials or case reports, significantly limiting generalizability. Additionally, compounded formulations differed widely across investigations, with variable strengths, vehicles, and application schedules.

Despite these limitations, topical metformin consistently demonstrated a favorable tolerability, clinically meaningful improvements across several dermatologic conditions, low systemic risk, and practical compounding feasibility. This profile supports the viability of metformin as a topical therapy, particularly in patients seeking alternatives to less tolerable or more toxic regimens, or those suffering from difficult-to-manage and treatment-resistant chronic conditions. Metformin maintains a mechanistic rationale for anti-inflammatory and wound-healing effects. However, standardization of dosing, vehicle selection, and application frequency remains a critical need. Future investigations should prioritize randomized controlled trials with consistent formulations, longer follow-up periods, and patient-reported outcomes to establish clinical protocols. For wound healing and scar modulation, early findings indicate anti-inflammatory, anti-fibrotic, and growth factor–modulating effects, but optimal dose-response relationships remain undefined.

As compounded topical metformin therapies gain viability in medical practice, topical metformin represents an emerging option that balances mechanistic sophistication with practical advantages such as safety, affordability, and formulation flexibility. Prescribers may consider topical metformin when patients experience irritation with standard agents, require steroid-sparing options, or would benefit from targeted therapy with minimal systemic exposure. Pharmacists and prescribers should collaborate closely to ensure evidence-based application, appropriate patient counseling, and monitoring for tolerability and effectiveness. Real-world data will ultimately determine whether topical metformin warrants broader clinical adoption.

Conclusion

Compounded topical metformin shows promising therapeutic potential across chronic periodontitis, melasma, wound

healing, and CCCA. Current evidence suggests that topical delivery is well tolerated, mechanistically plausible, and capable of producing clinically meaningful improvements. Ideally, compounded topical metformin would be evaluated using a consistent formula in varying strengths, compared with placebo, with check-ins at various points throughout the treatment process. Although further evaluation will continue to improve evidence-based prescribing of compounded topical metformin, it currently stands as an affordable, safe, and mechanistically rational treatment option for chronic periodontitis, diabetic wound healing, melasma, and hair regrowth.

Large, multicenter randomized trials employing standardized formulations are needed to support broad clinical adoption. Until then, topical metformin represents a mechanistically sound, affordable, and potentially valuable option when prescribed and compounded responsibly.

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