



EFFECTS OF METFORMIN ON SKIN INFLAMMATION AND HYPERPIGMENTATION A NARRATIVE REVIEW OF MOLECULAR MECHANISMS AND CLINICAL EVIDENCE

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ABSTRACT

Metformin shows anti-inflammatory and antimelanogenic activity in experimental models, but the mechanisms and strength of evidence differ by context. This is relevant to hyperpigmentation, where inflammation and melanocyte activation may intersect. To synthesize evidence on metformin in cutaneous inflammation and hyperpigmentation, focusing on mechanisms, the inflammation-pigmentation interface, topical clinical data, and evidence gaps. Structured searches of PubMed/MEDLINE and Scopus were conducted from 10 September 2026 through 26 September 2026 using complementary inflammation, pigmentation, and topical/clinical search blocks. Of 433 records identified, 105 underwent detailed evaluation and 21 primary studies formed the core synthesis. Reporting followed SANRA principles. Metformin modulated NF- κ B, AMPK/SIRT1-NLRP3, mTOR/p70S6K, IL-23-related, ROS, and immunometabolic pathways in experimental inflammatory models. Melanocyte studies showed inhibition of cAMP-CREB-MITF signaling, melanogenic enzymes, and melanosome transfer. Human evidence is concentrated in small, heterogeneous melasma trials; direct clinical evidence for PIH is lacking. Metformin has plausible effects on cutaneous inflammation and melanogenesis, but clinical evidence remains limited. Topical metformin should be considered investigational pending standardized formulations, pharmacokinetic data, longer safety follow-up, and adequately powered comparator trials.

Keywords: hyperpigmentation; melanogenesis; melasma; metformin; post-inflammatory; skin inflammation

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INTRODUCTION

Pigmentary disorders are common and carry psychosocial burden. A multinational survey of 48,000 adults in 34 countries reported pigmentary disorders in 50%; PIH and melasma were reported by 14.8% and 10.9%, respectively (Passeron, 2026). PIH is relevant because inflammatory injury can intersect with melanocyte activation (Maghfour et al., 2022). Melasma and PIH are treated with photoprotection, topical agents, and procedures. Hydroquinone, including triple-combination therapy, remains a benchmark for melasma, although irritation and uncommon exogenous ochronosis are concerns (Sarkar, 2023), (Shivaram dkk., 2024). These limitations motivate alternative approaches.

Metformin is of interest because its cellular effects extend beyond glucose lowering. Experimental studies report both inflammatory and melanogenic effects, but these should not be treated as one mechanism. Antimelanogenic activity involved cAMP/CREB/MITF and melanogenic enzymes independently of AMPK (Lehraiki, 2014), whereas anti-inflammatory effects involve NF- κ B, AMPK/SIRT1-NLRP3, mTOR, IL-23-related, oxidative, and immunometabolic pathways (Chang & Choi, 2020), (Ba, 2019), (Tsuji, 2020), (Y. Liu dkk., 2016), (Matsuda-Taniguchi, 2021).

Clinical implications remain uncertain. Inflammatory evidence is mainly preclinical or translational, while human pigmentation evidence consists of small, heterogeneous melasma trials. Reducing inflammatory mediators does not establish prevention or treatment of PIH. This review addresses

three questions: evidence for cutaneous anti-inflammatory effects; direct effects on melanogenesis and pigment transfer; and whether clinical data support topical metformin for hyperpigmentation, including comparison with hydroquinone-containing therapy.

METHOD

This narrative review followed SANRA principles for explicit aims, literature-search description, referencing, scientific reasoning, and endpoint reporting (Baethge dkk., 2019). It was not registered or conducted as a systematic review. Searches in PubMed/MEDLINE and Scopus were conducted from 10 September 2026 through 26 September 2026. Complementary blocks covered inflammation (including NF- κ B, NLRP3, AMPK, mTOR and cytokines), pigmentation (melasma, PIH, melanogenesis, MITF and tyrosinase), and topical/clinical use (cream, lotion, microneedling and delivery terms). Syntax was adapted to each database. The searches yielded 433 records (237 Scopus; 196 PubMed/MEDLINE). After deduplication and title/abstract relevance assessment, 105 publications underwent detailed evaluation; 21 primary studies formed the core synthesis and 84 were excluded at this stage. The remaining 328 were not advanced, and duplicate versus title/abstract exclusion counts were not retrospectively separated. Eligible studies included in vitro, ex vivo, animal, observational, and interventional human research on cutaneous inflammation, melanogenesis/hyperpigmentation, topical delivery, or clinical outcomes. Studies without dermatologic endpoints and case reports were excluded. Reviews and meta-analyses were used for context but not counted among the 21 core studies; evidence was interpreted separately by study type.

Table 1.
Narrative-review evidence selection

Search/selection stage	Number
Scopus records identified	237
PubMed/MEDLINE records identified	196
Total records identified	433
Retained for detailed evaluation	105
Excluded after detailed assessment	84
Core primary studies included	21

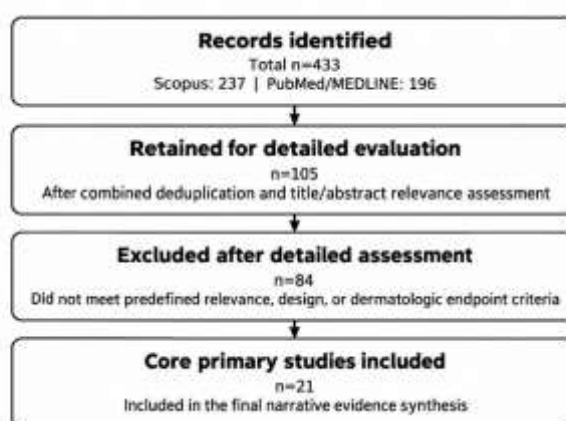


Figure 1. Narrative-review evidence selection flow. The count of 328 records not advanced is intentionally not partitioned into duplicates versus title/abstract exclusions because those subcounts were not preserved in the verified search log.

RESULT

Pharmacological and Formulation Considerations

Metformin is hydrophilic and its pharmacology is context dependent. Mitochondrial, AMPK, mTOR, and cAMP effects vary with cell type, concentration, and exposure duration; some in vitro studies use concentrations far above systemic levels, limiting translation. Topical delivery is limited by metformin hydrophilicity and charge. Hyaluronic-acid-coated chitosan/gelatin nanoparticles

increased skin deposition versus free metformin in an experimental model (Ebrahimnejad, 2023), supporting formulation optimization but not a clinically effective skin concentration. Oral safety cannot be assumed to establish topical safety because local irritation, barrier effects, penetration, excipients, and systemic absorption may differ. Topical studies should therefore measure local tolerability and systemic exposure.

Metformin and Cutaneous Inflammation

Keratinocyte NF- κ B signaling

In TNF- α -stimulated HaCaT keratinocytes, metformin reduced TNF- α , IL-6, IL-8 and IL-1 β , limited p65 nuclear localization, and inhibited NF- κ B activity and I κ B α degradation (Y. Liu dkk., 2016), supporting an NF- κ B-related mechanism. Because the model is immortalized and in vitro, the findings support pathway plausibility rather than a clinical dose or disease-specific efficacy.

AMPK/SIRT1-NLRP3 inflammasome signaling

(Tsuji, 2020) found that metformin reduced IL-1 β /caspase-1 signaling and several inflammatory mediators in primary human keratinocytes; AMPK/SIRT1 were implicated. Oral metformin also improved an imiquimod psoriasis-like mouse model (Tsuji, 2020). The combination of primary keratinocytes and an animal model strengthens mechanistic support, but it remains preclinical and does not establish clinical efficacy in psoriasis.

mTOR/p70S6K and the problem of experimental concentration

(Y. Liu dkk., 2016) reported reduced IL-6, TNF- α , VEGF and mTOR/p70S6K phosphorylation in HaCaT cells (Y. Liu dkk., 2016). However, 50 mM metformin reduced survival and increased apoptosis, so high-dose effects may not reflect selective anti-inflammatory signaling. Future mechanistic studies should anchor concentrations to measured skin exposure from clinically plausible formulations.

Dendritic-cell IL-36 γ -NFKBIZ-IL-23 signaling

In murine dendritic cells, metformin reduced NF- κ B phosphorylation, Nfkbiz and IL-23 responses to IL-36 γ (Matsuda-Taniguchi, 2021). This supports an IL-23/IL-17-related mechanism but is limited to a murine cellular model.

Rosacea: oxidative stress, angiogenesis, and MAPK-NF- κ B

In rosacea models, metformin reduced inflammation, angiogenesis, ROS and MAPK-NF- κ B activation (Li, 2021). The evidence remains experimental, with no randomized patient-level efficacy data.

Hidradenitis suppurativa as a translational immunometabolic model

In HS, (Jennings dkk., 2020) retrospectively reported subjective clinical response in 68% of 53 patients treated with oral metformin, but the uncontrolled design and subjective outcome limit causal inference (Jennings dkk., 2020). (Hambly dkk., 2023) compared 20 metformin-treated HS patients with 20 controls; fasting insulin and some metabolic markers improved, while inflammatory markers generally trended lower without consistent significance (Hambly dkk., 2023). (Petrasca, 2023) found reduced inflammatory cytokines/chemokines and glycolytic-gene expression in HS-related PBMC and ex vivo skin models, with NLRP3 and AMPK-mTOR involvement (Petrasca, 2023). These are translational but not randomized efficacy data.

Disease-level evidence and limits of generalization

(Tseng, 2023) compared 234,585 metformin initiators with 125,921 comparators and found lower hazards for a composite of immune-mediated skin diseases (Tseng, 2023). This observational association cannot establish mechanism or causality and should not be generalized to all dermatoses. In diabetic rats with psoriasis-like lesions, systemic and topical metformin increased

AMPK and reduced KGF/STAT3 and IL-17 receptor-related expression (Hassan, 2025); these findings remain preclinical. Overall, inflammatory evidence ranges from mechanistic and animal studies to small HS cohorts and population associations. A powered randomized trial linking clinical benefit to validated skin exposure is lacking.

The Inflammation-Pigmentation Interface and Post-Inflammatory Hyperpigmentation

PIH links inflammation and pigmentation. Cytokines, eicosanoids, endothelin-1, stem cell factor, oxidative stress, and cell-to-cell signaling can alter melanocyte activity after skin injury (Maghfour dkk., 2022), (Markiewicz dkk., 2022), with persistent pigment changes particularly relevant in darker phototypes. Metformin is therefore mechanistically interesting, but convergence of anti-inflammatory and antimelanogenic effects remains hypothetical. Neither reduced inflammatory mediators nor reduced melanogenesis in models proves PIH prevention in patients. No controlled clinical study identified metformin specifically for PIH after acne, dermatitis, procedures, or other inflammatory injury. Thus PIH should be considered a research indication rather than an established metformin indication (Markiewicz dkk., 2022), (Kashetsky dkk., 2024).

Metformin and Hyperpigmentation: Direct Melanocyte and Tissue Evidence

cAMP-CREB-MITF signaling and melanogenic enzymes

(Lehraiki, 2014) showed reduced melanin, cAMP, CREB phosphorylation, MITF, tyrosinase, DCT and TYRP1 in melanoma cells and normal melanocytes, with supporting effects in reconstructed epidermis, skin biopsies and mouse tail (Lehraiki, 2014). The antimelanogenic effect was reported as AMPK-independent. (X. Liu, 2025) found reduced melanin, tyrosinase activity, melanogenesis genes, dendrite formation and melanosome-transfer markers in zebrafish and melanocyte models, implicating cAMP-MITF and Rho GTPase pathways (X. Liu, 2025).

In vivo ultraviolet/hormonal hyperpigmentation models

In a 2026 UV/progesterone mouse chloasma model, topical metformin reduced CREB1/MITF, melanocyte counts and tyrosinase activity (Jiang dkk., 2026). Hormonal co-induction and a laser treatment arm limit isolation of a pure UV effect.

Context-dependent pigment biology: ATG7 and melanocyte senescence

Kim et al. (2026) found that metformin restored ATG7-related autophagy, reduced oxidative stress and delayed senescence in UVB-stressed melanocytes (Kim, 2026).

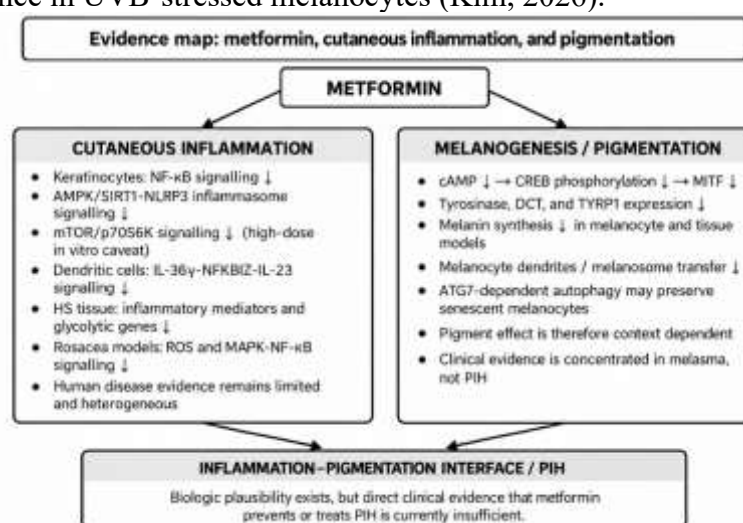


Figure 2. Evidence map linking metformin to cutaneous inflammation and pigmentation; direct clinical evidence for PIH remains insufficient

This addressed hypopigmented ageing-related skin rather than hyperpigmentation. Together, these findings indicate context dependence: metformin may suppress excessive melanogenesis in one

setting while preserving stressed melanocyte function in another. It should not be characterized as a universal skin-lightening agent.

Clinical Evidence for Topical Metformin in Melasma

Conventional topical formulations without microneedling

A randomized double-blind trial of 15% topical metformin versus placebo in 60 patients with melasma did not show a clear early superiority signal; short follow-up and limited reporting constrain interpretation (Ali Mapar dkk., 2019). In 40 patients, 30% metformin lotion and hydroquinone-containing triple-combination cream both improved melasma over 8 weeks, with no significant between-group difference (Banavase Channakeshavaiah & Andanooru Chandrappa, 2020). The small study was not designed for noninferiority or equivalence. (AboAlsoud dkk., 2022) likewise found substantial MASI reduction with 30% metformin cream and triple-combination cream in about 40 patients, without a significant between-group difference (AboAlsoud dkk., 2022). Equivalence and long-term safety were not established. A 2023 meta-analysis of three randomized trials (140 participants) judged the evidence limited by small samples and high risk of bias, with low or very-low certainty for several comparisons (Mongkhon dkk., 2023).

Microneedling-assisted delivery

In 30 women, microneedling plus metformin produced a reported 48.29% Hemi-MASI reduction versus 37.19% with microneedling plus vitamin C (Mahmoud dkk., 2024). Both sides received an active procedure. In 18 patients, microneedling plus metformin produced lower post-treatment Hemi-mMASI than microneedling plus placebo (2.39 ± 1.42 vs 4.72 ± 1.27) (Bessar dkk., 2024). The sample was very small and both sides received microneedling. In 45 women, a 2025 randomized study found smaller mMASI reduction with microneedling-assisted metformin than with tranexamic acid or modified Kligman formula (Al Mohammady dkk., 2025), highlighting comparator and delivery heterogeneity. Clinical studies therefore comprise conventional topical and procedure-assisted delivery. Trials differ in concentration, vehicle, duration, co-intervention, outcome measures and photoprotection, limiting cross-study comparison.

Table 2.

Core evidence matrix of 21 primary studies

Study / context	Key finding	Main limitation
(Lehraiki, 2014) Melanogenesis	Reduced cAMP and CREB phosphorylation, MITF, tyrosinase, DCT and TYRP1; reduced melanin. Antimelanogenic effect reported as AMPK-independent.	Preclinical; clinical efficacy and topical exposure not established.
(Ba, 2019) Psoriasis-related keratinocyte inflammation	Reduced TNF- α , IL-6, IL-8 and IL-1 β ; inhibited p65 nuclear localization, NF- κ B transcription and I κ B α degradation.	Immortalized cell line; in vitro concentration/exposure.
(Tsuji, 2020) Psoriasis-related inflammation	Reduced IL-1 β /caspase-1 signaling and multiple chemokines/S100 proteins; AMPK/SIRT1 implicated; improved psoriasis-like mouse phenotype.	Preclinical; no randomized patient trial.
(Y. Liu dkk., 2016) Keratinocyte hyperproliferation / psoriasis	Reduced IL-6, TNF- α , VEGF and p-mTOR/p70S6K.	High metformin concentrations caused reduced survival/apoptosis, confounding pathway specificity.
(Matsuda-Taniguchi, 2021) IL-23/IL-17 axis	Metformin reduced NF- κ B phosphorylation, Nfkbiz and IL-23 response to IL-36 γ .	Murine cellular model only.
(Li, 2021) Rosacea	Reduced inflammatory infiltration, angiogenesis, ROS and MAPK-NF- κ B activation in rosacea models.	Experimental, not randomized clinical evidence.

Study / context	Key finding	Main limitation
(Jennings dkk., 2020) Hidradenitis suppurativa	Subjective clinical response reported in 68%; 25% had no improvement.	Uncontrolled, retrospective, subjective outcomes.
(Hambly dkk., 2023) Hidradenitis suppurativa	Improved fasting insulin and several CV risk biomarkers; inflammatory mediators mostly trended lower.	Small observational study; cytokine differences often nonsignificant.
(Petrasca, 2023) Hidradenitis suppurativa	Reduced inflammatory cytokines/chemokines and glycolytic genes; NLRP3 and AMPK-mTOR implicated.	Observational patient comparison plus ex vivo experiment; not an efficacy RCT.
(Tseng, 2023) Multiple non-cancer skin diseases	Metformin initiation associated with lower hazards for immune-mediated skin diseases.	Diabetes population; residual confounding; association cannot establish mechanism or causality.
(Hassan, 2025) Psoriasis	Topical/systemic metformin increased AMPK and reduced KGF/STAT3 and IL-17 receptor-related expression.	Animal model; limited human translation.
(Ebrahimnejad, 2023) Topical delivery	Hyaluronic-acid-coated chitosan/gelatin nanoparticles increased metformin skin deposition versus free drug.	Delivery study; not a clinical pigmentation or inflammatory efficacy trial.
(X. Liu, 2025) Melanogenesis / transfer	Reduced melanin, tyrosinase, cAMP-MITF signaling, dendrites and melanosome-transfer-related genes.	Preclinical; clinical exposure-response unknown.
(Jiang dkk., 2026) Hyperpigmentation	Topical metformin reduced CREB1/MITF expression, melanocyte count and tyrosinase activity.	Hormonal co-induction and procedural combination limit isolation of pure UV effect.
(Kim, 2026) Melanocyte senescence / hypopigmentation	Metformin restored ATG7-related autophagy, reduced oxidative stress and delayed melanocyte senescence.	Addresses preservation of melanocyte function, not hyperpigmentation treatment.
(Ali Mapar dkk., 2019) Melasma	15% topical metformin compared with placebo; limited evidence of a clear early between-group superiority signal.	Short follow-up and limited reporting.
(Banavase Channakeshavaiah & Andanooru Chandrappa, 2020) Melasma	30% metformin lotion and hydroquinone-containing triple-combination cream both improved; between-group difference not statistically significant.	Small, 8-week study; not designed for formal noninferiority/equivalence.
(AboAlsoud dkk., 2022) Melasma	30% metformin cream and triple-combination cream produced substantial MASI reduction; no significant between-group difference.	Small, short trial; cannot establish equivalence or long-term safety.
(Mahmoud dkk., 2024) Melasma	Microneedling + metformin produced 48.29% Hemi-MASI improvement vs 37.19% with microneedling + vitamin C.	Small split-face study; both sides received an active procedure.
(Bessar dkk., 2024) Melasma	Microneedling + metformin yielded lower post-treatment Hemi-mMASI than microneedling + placebo.	Very small sample; procedural co-intervention.
(Al Mohammady dkk., 2025) Melasma	mMASI reduction was smaller with microneedling + metformin than with microneedling + tranexamic acid or modified Kligman formula.	Small groups and heterogeneous treatment modalities.

DISCUSSION

Comparison with Hydroquinone and Triple-Combination Therapy

Hydroquinone and hydroquinone-containing triple-combination therapy have substantial clinical evidence supporting their use in melasma management (Sarkar, 2023). Triple-combination therapy generally combines hydroquinone, a retinoid, and a topical corticosteroid to target melanogenesis

while addressing epidermal turnover and treatment-associated inflammation. Nevertheless, treatment selection requires consideration of efficacy, tolerability, photoprotection, and the chronic, recurrent nature of melasma (Sarkar, 2023).

Hydroquinone-based treatments also have limitations. Local irritation may affect treatment tolerability, while exogenous ochronosis is an uncommon but clinically important complication associated with prolonged or inappropriate hydroquinone use. In a systematic review of 126 reported patients with hydroquinone-associated exogenous ochronosis, (Ishack & Lipner, 2022) found that cases were frequently associated with prolonged use; the median reported duration was five years. These findings support the importance of appropriate prescribing and monitoring, but the case-based evidence does not establish the incidence of ochronosis among all hydroquinone users. Consequently, the possibility of adverse effects provides a rationale for investigating alternative treatments, rather than proof that metformin has a superior safety profile.

Clinical evidence for topical metformin in melasma remains limited. (Banavase Channakeshavaiah & Andanooru Chandrappa, 2020) conducted a randomized controlled study involving 40 patients who received either 30% metformin lotion or hydroquinone-containing triple-combination therapy for eight weeks. The investigators reported no statistically significant difference between groups in the improvement categories assessed, although adverse events were reported in three patients receiving triple-combination therapy and none receiving metformin. A subsequent randomized study involving 40 patients also compared 30% metformin cream with triple-combination cream over eight weeks. (AboAlsoud dkk., 2022) reported reductions in the Melasma Area and Severity Index (MASI) in both groups, without a statistically significant between-group difference.

These individual trials should be interpreted alongside the systematic review and meta-analysis by (Mongkhon dkk., 2023), which included three randomized controlled trials involving 140 patients. The review found that 15% topical metformin reduced MASI scores compared with placebo in one trial, while the pooled comparison of 30% topical metformin with triple-combination cream showed no statistically significant difference after eight weeks. Adverse events were numerically fewer among participants receiving metformin, but the difference was not statistically significant. The small number of included trials, limited sample sizes, and short follow-up periods restrict the certainty and generalizability of these findings.

Importantly, failure to detect a statistically significant difference does not establish therapeutic equivalence or noninferiority. A noninferiority trial requires a prespecified and clinically justified margin, appropriate sample-size calculations, and confidence intervals demonstrating that the treatment difference does not exceed the permitted margin. The existing evidence therefore supports further evaluation of topical metformin but does not establish that it is equivalent or superior to hydroquinone monotherapy or standardized triple-combination therapy.

The safety comparison also remains provisional. Small studies with short follow-up are unlikely to characterize uncommon adverse events or delayed complications adequately. Furthermore, findings from a particular formulation cannot necessarily be generalized to other formulations because the vehicle, concentration, pH, application frequency, and treated surface area may influence local exposure and tolerability. Although metformin has been investigated in several dermatological conditions, the broader dermatology literature also illustrates the importance of distinguishing evidence from different routes of administration and clinical indications (Badr dkk., 2013). Oral safety experience should not be treated as a substitute for dedicated evaluation of topical formulations. From a clinical perspective, topical metformin is a promising investigational approach because its potential biological effects extend beyond pigmentation-related pathways. However, the clinical relevance of these mechanisms depends on whether effective concentrations can reach the target tissue without causing unacceptable local effects. At present, the evidence is most directly

relevant to melasma; it should not be generalized automatically to post-inflammatory hyperpigmentation (PIH) or other inflammatory dermatoses. The next step is to determine whether topical metformin produces reproducible, clinically meaningful benefits under standardized conditions and whether any benefits persist after treatment discontinuation.

Research Gaps and Future Directions

Several research priorities must be addressed before topical metformin can be considered an established treatment for melasma or PIH. First, future clinical trials should recruit larger and more representative samples, use prospective registration, and include sufficiently long follow-up to assess sustained improvement and recurrence. The current clinical evidence base is small: the systematic review by (Mongkhon dkk., 2023) identified only three randomized controlled trials, each with limited follow-up. Since melasma is chronic and recurrent, short-term pigment reduction alone is insufficient to establish durable clinical benefit. Trials should distinguish initial response from maintenance of improvement and recurrence after treatment discontinuation.

Second, topical pharmacokinetics and formulation characteristics require systematic investigation. Studies should clearly specify metformin concentration, salt form, vehicle, pH, application frequency, and delivery system. They should also measure skin exposure and, where appropriate, systemic absorption. These data are necessary to determine whether experimental concentrations can be achieved in human skin under practical conditions and whether differences between studies reflect the active compound or formulation characteristics.

Third, mechanistic findings should be interpreted in relation to clinically relevant exposure. Experimental studies investigating inflammatory and metabolic pathways can generate hypotheses about the potential effects of metformin on skin inflammation and pigmentation. Nevertheless, pathway modulation in cultured cells does not automatically predict clinical benefit. Future studies should include dose–response assessments, cytotoxicity controls, and concentrations justified by measured or plausibly achievable skin exposure. This approach would help distinguish specific pharmacological effects from nonspecific effects associated with excessive concentrations.

Fourth, the proposed relationship between inflammation and pigmentation requires direct clinical testing. Randomized trials should evaluate metformin for the treatment or prevention of PIH following clearly defined inflammatory triggers. These studies should specify the underlying trigger, baseline pigmentation, skin phototype, timing of treatment, and concomitant therapies. Treatment of established PIH and prevention of PIH should be investigated as separate questions because their clinical objectives and treatment timing differ. Current clinical trials in melasma cannot independently establish effectiveness for PIH.

Fifth, comparative trials should use clinically relevant active comparators and prespecified statistical criteria. For melasma, these may include hydroquinone monotherapy or a standardized hydroquinone-containing triple-combination regimen, depending on the research question. Investigators should define superiority or noninferiority objectives in advance and report adherence, photoprotection, rescue therapy, and adverse events consistently. Evidence syntheses of melasma treatments emphasize that comparisons across topical interventions depend on the availability and comparability of well-designed clinical studies (Chang & Choi, 2020; Mongkhon dkk., 2023).

Sixth, outcome measurement should be harmonized across studies. MASI or modified MASI (mMASI), objective colorimetry, standardized photography, patient-reported outcomes, and recurrence measures can provide complementary information. Measurement conditions should be standardized, including lighting and photographic procedures. Patient-reported outcomes should assess perceived improvement, treatment satisfaction, irritation, and quality of life where

appropriate. Consistent outcomes and follow-up intervals would improve comparisons across trials and help determine whether observed changes are clinically meaningful.

Seventh, inflammatory dermatoses should be investigated separately rather than treated as a single clinical category. Metformin has been discussed in relation to several dermatological conditions, including psoriasis and hidradenitis suppurativa, but evidence from one indication cannot establish effectiveness in another (Badr dkk., 2013). These conditions differ in pathophysiology, tissue environment, clinical endpoints, and treatment requirements. Disease-specific randomized trials are therefore needed before mechanistic findings can be translated into clinical recommendations.

Eighth, future studies should deliberately include darker skin phototypes and Southeast Asian populations. Study reports should describe skin phototype and relevant demographic characteristics in sufficient detail to assess the applicability of findings across populations. Where subgroup comparisons are planned, investigators should specify them prospectively and ensure that the study design supports meaningful interpretation. Population representation is particularly important when evaluating pigmentation outcomes, but it should not be treated as evidence of differential efficacy without appropriate analyses.

Finally, long-term local safety requires dedicated dermatologic pharmacovigilance. Oral metformin experience cannot substitute for evidence on topical formulations because route of administration and local tissue exposure differ. Safety assessment should include irritation, allergic contact reactions, treatment discontinuation, changes in skin-barrier function, and systemic exposure where relevant. Larger studies and longer observation periods are needed to characterize uncommon or delayed effects. Overall, available evidence supports continued investigation of topical metformin but does not yet establish it as an equivalent or superior alternative to established depigmenting treatments. The existing clinical literature provides preliminary evidence of potential benefit in melasma, while important uncertainties remain regarding long-term efficacy, formulation, safety, and applicability to PIH. Progress will depend on connecting mechanistic findings to realistic skin exposure, conducting adequately powered comparative trials, standardizing clinical outcomes, and establishing long-term safety.

CONCLUSION

Current evidence supports metformin effects on several inflammatory pathways, including NF- κ B, AMPK/SIRT1-NLRP3, mTOR and IL-23-related signaling, while melanocyte studies show inhibition of cAMP-CREB-MITF-related melanogenesis and melanosome transfer. Evidence strength varies by endpoint. Human evidence is limited to small, heterogeneous melasma trials. Nonsignificant differences from hydroquinone-containing triple-combination therapy do not establish equivalence or noninferiority, and direct clinical evidence for PIH or randomized efficacy in inflammatory dermatoses remains insufficient. Metformin should therefore remain an investigational topical candidate rather than an established replacement for standard therapy. Priority research should combine standardized formulations, topical pharmacokinetics, adequately powered comparator trials, longer safety follow-up and direct evaluation of the inflammation-pigmentation interface.

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