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 ORIGINAL ARTICLE

Isobutylamido Thiazolyl Resorcinol (Thiamidol) for Combatting Hyperpigmentation: A Systematic Review of Clinical Studies

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ABSTRACT

Background: Tyrosinase is the rate-limiting enzyme of melanogenesis and thus an ideal inhibitory target for treating hyperpigmentation. There are many commercially available tyrosinase inhibitors with limited clinical efficacy. A recent screen of 50,000 compounds found isobutylamido thiazolyl resorcinol (ITR) to be the most potent inhibitor of human tyrosinase.

Objective: To summarize the current evidence on the efficacy and adverse effects of ITR in treating hyperpigmentation.

Methods: A literature search was conducted using PubMed and Google Scholar databases in June 2022. Fourteen clinical studies investigating the use of topical ITR in hyperpigmentation treatment or prevention were identified.

Results: Most studies (n=13) investigated topical ITR as a treatment, while only one investigated ITR as a preventative measure against hyperpigmentation. All studies (n=14) found ITR to provide statistically significant improvements to hyperpigmentation conditions, including facial hyperpigmentation (n=3), melasma (n=5), post-inflammatory hyperpigmentation (PIH) (n=3), and UV-induced hyperpigmentation (n=3). Evidence suggests that the effective dosage and duration of topical ITR appears to be 0.1% to 0.2% ITR 2 to 4 times daily for 12 to 24 weeks. Successful prevention of UVB-induced hyperpigmentation has been seen following twice-daily topical ITR application for 3 weeks ($P<0.001$).

Conclusion: Topical ITR can significantly reduce hyperpigmentation; however, the evidence for its use is limited. Further investigation is warranted to identify the optimal dosage and application schedule of ITR, as well as compare the efficacy of ITR vs hydroquinone to determine if ITR is superior to the current standard of care.

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INTRODUCTION

Hyperpigmentation, the overproduction of melanin within the skin, is estimated to be the 11th most prevalent disorder seen in dermatology practices and the most frequent skin complaint among patients aged 40 to 45 years.[1,2] This condition predominantly affects women with Fitzpatrick skin types (FST) III to V and can be cosmetically disfiguring, alter psychosocial well-being, and adversely impact the quality of life in affected individuals.[3,4]

Current treatment options – including topicals (eg, hydroquinone, arbutin, and kojic acid), oral agents (eg, cysteamine hydrochloride, melatonin, and tranexamic acid), chemical peels, and laser therapy – have varying efficacies, side effects, and may require lengthy treatment duration to achieve desired effects.[5] Hydroquinone is currently the criterion standard for hyperpigmentation treatment. However, its use is limited by several potential adverse effects including contact dermatitis, skin irritation, hypopigmentation, and, paradoxically, exogenous ochronosis (bluish-gray or black hyperpigmentation).[6,7] In fact, the European Union banned hydroquinone from cosmetic use due to its adverse effect profile.[6] There is therefore a need for clinically efficacious and safer alternative therapies for treating hyperpigmentation.

Tyrosinase, the rate-limiting enzyme of melanogenesis, is an attractive inhibitory target for treating hyperpigmentation (Figure 1).[6] While several tyrosinase inhibitors are already

FIGURE 1. ITR inhibits the rate-limiting step of melanogenesis.

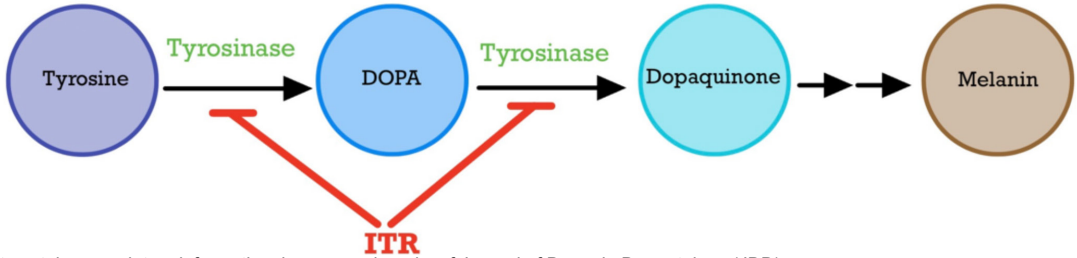
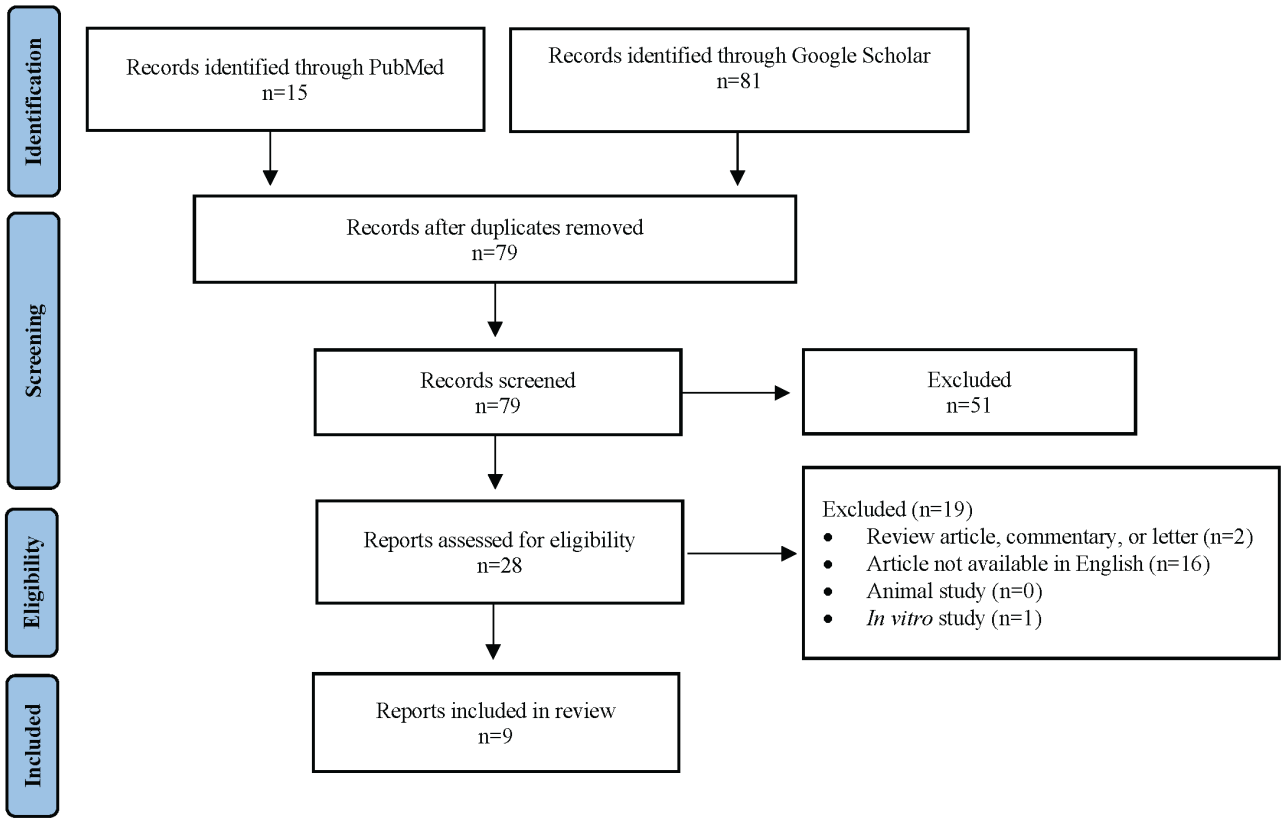


FIGURE 2. PRISMA diagram. Process of inclusion of studies



commercially available,[6] a recent screen of 50,000 compounds found isobutylamido thiazolyl resorcinol (ITR), a thiazolyl-resorcinol derivative, to be the most potent and clinically efficacious inhibitor of human tyrosinase.[6] To date, ITR has been shown to reduce facial hyperpigmentation, melasma, postinflammatory hyperpigmentation (PIH), and UV-induced hyperpigmentation. Herein, we summarize the current evidence on the efficacy of ITR and its adverse effects in treating hyperpigmentation disorders.

MATERIALS AND METHODS

A literature search was conducted in June 2022 on PubMed and Google Scholar databases for all clinical studies investigating ITR as an agent against hyperpigmentation. The following search term was used: "thiamidol" OR "isobutylamido thiazolyl resorcinol" OR "Isobutylene thiazolyl resorcinol" OR "thiazolyl resorcinol." This yielded 81 articles on Google Scholar and 15 on PubMed. The title and abstract of each article were screened (Figure 2). Exclusion criteria included (1) nonevidence-based studies (ie, review articles, commentaries, letters); (2) articles not available in English; (3) animal studies; and (4) in vitro studies.

RESULTS

Nine articles, accounting for a total of 14 clinical studies, investigating topical ITR as an agent against hyperpigmentation were identified (564 patients; age range 18-71 years). Most studies included participants with FST II to V (n=8), while 2 studies included either FST I or FST VI. Most studies (n=13) investigated ITR as a treatment, while 1 investigated ITR as a preventative measure against hyperpigmentation. All studies (n=14) found ITR to provide statistically significant improvements to hyperpigmentation conditions, including facial hyperpigmentation (n=3), melasma (n=5), PIH (n=3), and UV-induced hyperpigmentation (n=3) (Table 1).

Common Outcome Metrics

The Melasma Area and Severity Index (MASI), Facial Hyperpigmentation Severity Score on the malar area (FHSSm),[4] modified MASI (mMASI), and hemi-modified MASI (hMASI) are outcome measures for melasma or hyperpigmentation that are scored based on pigment darkness and area of involvement; note that the former two also are scored based on homogeneity. Relative lightness index (RL*I) is calculated by subtracting L*I of hyperpigmented skin from L*I of normal skin.[4] For all the

TABLE 1.

Clinical Studies Investigating Topical ITR as an Agent Against Hyperpigmentation Conditions

Hyperpigmentation Condition	Citation	Study Design	Participants, n=	Participant Sex	Participant Age Range (Mean Age)	Participant FST	Topical ITR Dosage & Application Schedule	Study Findings	Serious Adverse Effects
Facial Hyperpigmentation (n=3)	[8]	RCT, Split-face, Double-blind	34	F	25-64 (49.5)	II-IV (19), not provided (15)	ITR, BID or QID x 12 weeks	QID ITR significantly improved hyperpigmentation more than BID (P<0.001).	N/A
	[8]	Open-label, single-arm, observational	83	82F, 1M	27-71 (44.29)	I-IV (67), not provided (16)	ITR, 1 layer in AM & 2 layers in PM x 12 weeks	12-week use of an ITR-containing 3 product regimen significantly improved hyperpigmentation (P≤0.001).	N/A
	[4]	RCT, split-face, evaluator-blind	24	22F, 2M	>18 (48.04)	III-IV	0.15% ITR, BID x 12 weeks	Compared to laser monotherapy at 4 weeks, the 0.15% ITR-laser combined therapy significantly improved hyperpigmentation (P<0.05).	N/A
Melasma (n=5)	[9]	RCT, double-blind	48	F	38-64 (53)	III-V	ITR, 2 layers in AM & 1 layer in PM x 24 weeks	ITR-containing regimen significantly reduced hyperpigmentation more than ITR-free regimen at all points in time (P<0.001-0.043).	N/A
	[3]	RCT, split-face, evaluator-blind	31	F	29-63 (52)	N/A	0.2% ITR, BID x 12 weeks	ITR significantly reduced hyperpigmentation compared to baseline (P≤0.001). Control had no change from baseline.	ITR did not worsen melasma, control induced worsening melasma in 12.9% of participants.
	[3]	RCT, split-face, double-blind	28	F	31-65 (50.6)	N/A	0.2% ITR, BID x 12 weeks	ITR significantly reduced hyperpigmentation more than hydroquinone (P≤0.001).	ITR did not worsen melasma, hydroquinone led to worsening melasma in 10% of participants.
	[10]	RCT, evaluator-blind	50	F	18-50 (43)	II-V	0.2% ITR, BID for 90 days	ITR and hydroquinone both reduced hyperpigmentation (P<0.01). There was no difference between their reductions (P≥0.09).	Hydroquinone: mild erythema (8%), desquamation (8%), or a burning sensation (8%) (P= 0.235) ITR: 2 participants (8%) developed allergic contact dermatitis at days 60 and 75 of follow-up, and thus discontinued treatment.
	[11]	RCT, evaluator-blind	90	F	>18 (45.62)	IV-V	0.15% ITR, BID x 12 weeks	ITR monotherapy (P=0.027) and ITR-HA combined therapy (P=0.001) both significantly reduced hyperpigmentation compared to HA monotherapy in week 12. There was no convincing evidence that ITR-HA combined therapy was superior to ITR monotherapy.	Erythema (ITR-HA= 0%, ITR= 10%, HA= 3.3%), burning/stinging (ITR-HA= 6.7%, ITR= 16.7%, HA= 0%) and itching (ITR-HA= 6.6%, ITR= 0%, HA= 3.3%).[11]
PIH (n=3)	[12]	RCT	14	7F, 7M	28-58 (N/A)	II-III	ITR, BID x 12 weeks	At all points in time, ITR significantly improved suction blister-induced PIH compared to vehicle (P=0.009-0.034).	N/A
	[12]	RCT, single-blind	64	F	18-40 (N/A)	V	ITR, BID x 12 weeks	After 12 weeks, ITR significantly reduced (P=0.047) acne-induced PIH visibility compared to vehicle.	N/A
	[12]	Observational	29	28F & 4M were enrolled	18-50 (N/A)	V-VI	ITR, 2 layers in AM & 1 layer in PM x 12 weeks	ITR significantly improved acne-induced PIH at all points in time (P< 0.001) compared with baseline.	N/A
UV-induced hyperpigmentation (n=3)	[6]	RCT	17	F	56-71 (N/A)	N/A	0.2% ITR, BID x 12 weeks	ITR significantly lightened age spot pigmentation at all points in time compared to control (P<0.05 at weeks 4 and 8; P<0.01 at week 12).	N/A
	[6]	RCT	19	18F, 1M	58-70 (N/A)	N/A	0.1% ITR, BID for 12 weeks	ITR significantly reduced age spot pigmentation at weeks 8 and 12 vs baseline (P<0.05).	N/A
	[7]	RCT, split-arm, single-blind, pilot study	30	29F, 1M	>18 (34.77)	II-IV	0.15% ITR, 3 weeks	The ***preventive*** use of ITR 3 weeks before UVB-induced hyperpigmentation reduced the degree and duration of hyperpigmentation compared to no preventive treatment (ITR-treated arm mean lightness index [L*], 38.24 [±4.69] at baseline, 35.06 [±5.07] at 1 week after UVB irradiation; control arm L*, 38.41 [±4.23] at baseline, 32 [±4.86] at 1 week after UVB irradiation [P< 0.001]).	N/A

aforementioned metrics, a lower value indicates improvement/lightening of hyperpigmentation. In contrast, a higher mean lightness index (*L) value indicates improvement/lightening of hyperpigmentation.

Facial Hyperpigmentation

Three studies investigated ITR for facial hyperpigmentation treatment. First, a multicenter observational study (n=83) found that 12-week use of a ITR-containing 3-product regimen (SPF30 daycare, serum, and night cream) significantly improved mild-to-moderate facial hyperpigmentation (mMASI at baseline, 8.5 ± 3.9; mMASI at week 12, 3.6 ± 2.6; $P \leq 0.001$).[8] A split-face, double-blind, randomized controlled trial (RCT) (n=34) investigated the optimal frequency of ITR applications for mild-to-moderate facial hyperpigmentation treatment. Areas treated 4 times daily had statistically significant reductions ($P<0.001$) in hMASI at all points in time vs baseline (–0.72 ± 1.05 at week 4, –1.76 ± 1.69 at week 8, –2.43 ± 1.96 at week 12) and vs areas treated with ITR twice daily (–0.29 ± 0.69 at week 4, –0.84 ± 1.45 at week 8, –1.26 ± 1.52 at week 12).[8] A split-face, evaluator-blinded, prospective RCT (n=24) found that compared to Low-fluence Q-switched Nd:YAG 1064-nm laser (LFQS) alone, 0.15% topical ITR-LFQS combined therapy yielded a significantly greater reduction in both RL*I (62.5% vs 47.3% reduction, $P<0.05$) and FHSSm (54.4% vs 40.2% reduction; $P<0.05$).[4] However, ITR-LFQS combined therapy showed no significant effect on post-treatment maintenance.[4]

Melasma

Five studies investigated ITR for melasma treatment. A double-blind RCT of 48 participants with darker complexions (FST III-V) and moderate-to-severe melasma found 24-week use of an ITR-containing regimen (Dual Serum, SPF30 daycare, and night care) to yield a statistically significant reduction of MASI compared with an ITR-free regimen (–0.6 ± 0.6 at week 4, –2.4 ± 1.4 at week 8, –3.2 ± 2.1 at week 12, –3.6 ± 2.0 at week 16, –3.8 ± 2.3 at week 20, –4.2 ± 2.4 at week 24; $P<0.001$-0.043).[9] After the 24-week treatment phase, a 13- to 20-week regression phase with cessation of all treatment ensued. The MASI scores of participants in both the ITR and placebo group increased significantly during the regression phase yet remained below their respective baseline values. There was no significant difference between the groups after the regression phase.[9]

A split-face, evaluator-blinded study of 31 participants with mild-to-moderate melasma found that at week 12, twice-daily 0.2% ITR significantly reduced mMASI scores compared to baseline (baseline, 9.73 ± 4.45; week 12, 6.44 ± 4.42; $P \leq 0.001$), while twice-daily broad-spectrum sunscreen control (≥SPF30) induced no significant change in mMASI scores (baseline, 8.71 ± 4.59; week 12, 8.44 ± 4.95; $P \leq 0.001$).[3] ITR did not worsen melasma, while control led to worsening melasma in 12.9% of participants.[3]

A double-blind, split-face RCT of 28 participants compared twice-daily 0.2% ITR vs 2.0% hydroquinone in women with mild-to-moderate melasma.[3] Although ITR and hydroquinone both yielded statistically significant reductions in mMASI scores at 12 weeks compared to their respective baseline values, the improvement in the ITR side was significantly greater than that in the hydroquinone side ($P \leq 0.001$). Additionally, after 12 weeks, mMASI improvements were observed on the ITR-treated side in 78.6% of participants and on the hydroquinone side in 60.7% of participants. ITR did not worsen melasma, while hydroquinone led to worsening melasma in 10% of participants.

An evaluator-blinded RCT with 50 female participants compared twice-daily 0.2% ITR vs once-daily 4.0% hydroquinone for 90 days. Although the ITR and hydroquinone groups both yielded reductions in mMASI, Melasma Quality of Life scale, and color contrast scores ($P<0.01$), there was no difference between the groups in these reductions ($P \geq 0.09$).[10] Although neither intervention induced moderate or severe adverse events, mild adverse events did occur. Hydroquinone-treated participants experienced mild erythema (8%, $P=0.235$), mild desquamation (8%, $P=0.235$), or a mild burning sensation (8%, $P=0.235$), while no ITR-treated patients experienced these adverse events. However, 2 ITR-treated patients (8%) discontinued treatment as they developed allergic contact dermatitis at days 60 and 75 of follow-up.[10]

A prospective, evaluator-blind, RCT with 90 participants compared 0.15% ITR and hyaluronic acid (HA) combined therapy compared to both 0.15% ITR alone and HA alone in treating moderate-to-severe melasma.[11] The mMASI of all 3 groups significantly decreased at week 12 ($P<0.001$) compared to baseline. ITR-HA combined therapy ($P=0.001$) and ITR monotherapy ($P=0.027$) both yielded statistically significant reductions in mMASI in week 12 compared to the HA monotherapy group. Although the ITR-HA group had significantly lower melanin variation than the ITR group in week 4 ($P=0.027$), week 8 ($P=0.019$), and week 12 ($P=0.023$), there was no significant difference in the mMASI or average melanin level between the 2 groups.[11] Reported adverse effects include erythema (ITR-HA= 0%, ITR= 10%, HA= 3.3%) burning/stinging (ITR-HA= 6.7%, ITR= 16.7%, HA= 0%), and itching (ITR-HA= 6.6%, ITR= 0%, HA= 3.3%).[11]

PIH

Three studies investigated ITR as a treatment for either suction blister-induced PIH or acne-induced PIH.[12] A RCT induced 2 suction blisters on the upper arms of 14 participants. At 2 weeks, participants applied either an ITR-containing or vehicle formula bidaily for 12 weeks. Compared to vehicle-treated suction blisters, blisters treated with ITR yielded statistically significant improvements at all points in time ($P=0.034$, 0.023, 0.011, 0.009

for weeks 2, 5, 8, and 12, respectively). In fact, suction blisters treated with ITR for 2 weeks were, on average, lighter than blisters treated with the vehicle for 12 weeks.[12] In another RCT, 64 females with FST V and acne-induced PIH applied either an ITR-containing or vehicle formula bidaily on the entire face for 12 weeks. At 12 weeks, treatment with ITR resulted in a significant improvement in hyperpigmentation visibility when compared to vehicle (P=0.047).[12] Lastly, an observational study of 29 darker complected (FST V-VI) participants with acne-induced PIH found that an ITR-containing 3-product regimen (dual serum, SPF30 day cream, and night cream) yielded a statistically significant reduction in melanin index scores at all time points compared to baseline (melanin index score: 733.4 ± 138.8 at baseline, 654.1 ± 120.6 at week 4, 656.7 ± 116.1 at week 8, 632.7 ± 97.9 at week 12; P<0.001).[12]

UV-induced Hyperpigmentation

Three studies investigated ITR as an agent against UV-induced hyperpigmentation. A RCT (n=17) found that bidaily 0.2% ITR significantly lightened age spot pigmentation at all points in time compared to control (P<0.05 at weeks 4 and 8; P<0.01 at week 12). In fact, after 12 weeks of treatment, some ITR-treated age spots were indistinguishable from the surrounding normal skin.[6] Another RCT (n=19) found that bidaily 0.1% ITR yielded a statistically significant reduction in age spot pigmentation at weeks 8 and 12 compared to baseline (P<0.05).[6]

Beyond treatment, a randomized pilot study (n=30) investigated 0.15% ITR in preventing UVB-induced hyperpigmentation.[7] Following 3 weeks of ITR application on just one arm, UVB irradiation was used to induce 3 hyperpigmented spots on both arms of all participants. Pigmentary changes were then tracked for 4 weeks. Mean lightness index of the ITR-treated side remained significantly higher when compared to the control side at all points in time starting one week after UVB irradiation (weeks 4-7) (week 4: 32 ± 4.86 control side, 35.06 ± 5.07 ITR side (P<0.001); week 5: 33.2 ± 4.33 control side, 35.53 ± 5 ITR side (P=0.004); week 6: 34.98 ± 4.17 control side, 38.63 ± 10.21 ITR side (P<0.001); week 7: 36.25 ± 4.38 control side, 38.17 ± 5.01 ITR side (P=0.018)). Additionally, ITR treatment yielded earlier improvement, with the skin achieving baseline pigmentation 3 weeks post-UVB; while the control side remained significantly darker than its baseline value until the end of the study at 4 weeks post-UVB.[7]

DISCUSSION

Mechanism of Action

Tyrosinase is a copper-dependent enzyme that catalyzes 2 steps in melanogenesis: the conversion of tyrosine into dihydroxyphenylalanine (DOPA) and the oxidation of DOPA to dopaquinone.[13] Tyrosinase is the rate-limiting enzyme of melanogenesis, making it an ideal inhibitory target for hyperpigmentation treatment.[6] The clinical efficacy of many commercially available tyrosinase inhibitors (hydroquinone, kojic acid, and arbutin) remains limited partly because they were tested against mushroom tyrosinase, rather than human tyrosinase, as the target.[6] ITR, however, reduces melanin production by reversibly and competitively inhibiting human tyrosinase. The reversible inhibition of human tyrosinase by ITR is superior to the irreversible inhibition induced by hydroquinone.[6] In fact, a recent screen of 50,000 compounds found ITR to be the most potent and clinically efficacious inhibitor of human tyrosinase.[6]

Efficacy and Adverse Effects

The results of the studies included in this review suggest that ITR is an effective treatment for several hyperpigmentation conditions including melasma, PIH, and UV-induced hyperpigmentation. Given that hydroquinone is considered a gold standard treatment of hyperpigmentation disorders, 2 studies sought to directly compare its efficacy with that of ITR.[3,10] Arrowtiz et al found the 12-week use of bidaily 0.2% ITR to yield a larger mMASI score reduction compared to 2.0% hydroquinone (P≤0.001).[3] In contrast, Lima et al found similar mMASI score reductions after 90-day use of bidaily 2.0% ITR and once-daily 4.0% hydroquinone.[10] A potential explanation for the contrasting findings of these 2 studies is that they used vastly different concentrations of hydroquinone (4.0% vs 2.0%). Additional head-to-head studies are warranted to compare the relative efficacies of these 2 compounds. Nevertheless, studies to date suggest that ITR is at least as efficacious as hydroquinone in treating melasma and can therefore be thought of as a viable alternative, especially in those who have failed or cannot tolerate hydroquinone.

Arguably, the best way to reduce hyperpigmentation is by preventing its development in the first place. This is why sunscreen is a staple in any anti-hyperpigmentation regimen. Interestingly, Vachiramon et al reported that the application of 0.15% ITR bidaily for 3 weeks significantly prevented subsequent UVB-induced hyperpigmentation.[7] These findings are promising and suggest that ITR may have the ability to prevent the development or progression of other forms of hyperpigmentation. Further studies investigating ITR's effect on the prevention of melasma and PIH are warranted.

Two studies investigated the effect of ITR against hyperpigmentation recurrence.[4,9] After a 24-week treatment phase with either ITR or a placebo, Roggenkamp et al conducted a 13- to 20-week regression phase and found that although the MASI scores of both groups increased, they remained below their respective baseline values, suggesting some lasting effect.[9] However, there was no significant difference between the MASI scores of the 2 groups after the regression phase. These findings suggest that ITR does not provide lasting post-treatment results, but also does not induce a rebound effect after discontinuation

of treatment.[9] Similarly, a split-face study found no statistically significant difference in the melasma recurrence rate between sides treated with 0.15% ITR vs placebo at the end of follow-up.[4] ITR's lack of reported lasting results may be explained by its reversible inhibition of tyrosinase.[9] Nevertheless, maintenance use of ITR may be sufficient to reduce recurrence.

Most studies (n=12) reported no significant adverse effects or did not address any adverse effects induced by ITR. Two studies, however, did. Lima et al reported that 2 ITR-treated patients (8%) discontinued treatment as they developed allergic contact dermatitis at days 60 and 75 of follow-up.[10] Disphanurat et al reported erythema (10% of ITR-monotherapy participants), burning/stinging (6.7% and 16.7% of ITR-HA and ITR-monotherapy participants, respectively), and itching (6.6% of ITR-HA participants) as common adverse effects.[11] Although ITR, like most medications, may induce adverse effects, they appear to be less severe and less frequent than those induced by hydroquinone. However, more studies are needed to investigate the adverse effect profile of ITR.

Effective Dosage and Application Schedule

The effective dosage and duration of topical ITR appears to be 0.1% to 0.2% ITR 2 to 4 times daily for 12 to 24 weeks. Evidence suggests that applying topical ITR 4 times daily yields greater benefits than twice-daily application.[8] ITR is commercially available over the counter in Eucerin Anti-Pigment hyperpigmentation products.

Limitations

This review is limited by studies conducted primarily in female participants with FST II to V. More studies are needed investigating ITR as an agent against hyperpigmentation for men and people with FST I and VI. Additionally, 10 of the 14 studies included in this review were sponsored by and/or have authors who are employed by Beiersdorf AG, the company that has patented Thiamidol. Further investigation of ITR as a preventative measure against hyperpigmentation conditions is needed. Further investigation is warranted to identify the optimal dosage and application schedule of topical ITR, as well as compare the efficacy of ITR vs hydroquinone to determine if ITR is superior to the current standard of care.

CONCLUSION

There is a need for more clinically efficacious and safe hyperpigmentation therapy options. Based on current evidence, ITR may serve as a safe and efficacious adjunct or alternative therapeutic option for various hyperpigmentation disorders. However, larger rigorous studies are needed to validate these early results and to compare the safety and efficacy in head-to-head trials with more established compounds.

DISCLOSURES

The authors have no competing interests to declare.

REFERENCES

1. Fatima S, Braunberger T, Mohammad T, et al The role of sunscreen in melasma and postinflammatory hyperpigmentation. *Indian J Dermatol.* 2020;65(1). doi:10.4103/ijd.IJD_295_18
2. Charoo NA. Hyperpigmentation: Looking beyond hydroquinone. *J Cosmet Dermatol.* 2022;21(10):4133-4145. doi:10.1111/jocd.14746
3. Arrowitz C, Schoelermann AM, Mann T, et al. Effective tyrosinase inhibition by thiamidol results in significant improvement of mild to moderate melasma. *J Invest Dermatol.* 2019;139(8):1691-1698.e6. doi:10.1016/j.jid.2019.02.013
4. Vachiramon V, Leerunyakul K, Kositkuljorn C, et al. Combined isobutylamido thiazolyl resorcinol and low-fluence Q-switched Nd: YAG laser for the treatment of facial hyperpigmentation: A randomized, split-face study. *J Cosmet Dermatol.* 2021;20(6). doi:10.1111/jocd.13790
5. Nautiyal A, Wairkar S. Management of hyperpigmentation: Current treatments and emerging therapies. *Pigment Cell Melanoma Res.* 2021;34(6). doi:10.1111/pcmr.12986
6. Mann T, Gerwat W, Batzer J, et al. Inhibition of human tyrosinase requires molecular motifs distinctively different from mushroom tyrosinase. *J Invest Dermatol.* 2018;138(7):1601-1608. doi:10.1016/J.JID.2018.01.019
7. Vachiramon V, Kositkuljorn C, Leerunyakul K, et al. Isobutylamido thiazolyl resorcinol for prevention of UVB-induced hyperpigmentation. *J Cosmet Dermatol.* 2021;20(3). doi:10.1111/jocd.13615
8. Philipp-Dormston WG, Vila Echagüe A, Pérez Damonte SH, et al. Thiamidol containing treatment regimens in facial hyperpigmentation: An international multi-centre approach consisting of a double-blind, controlled, split-face study and of an open-label, real-world study. *Int J Cosmet Sci.* 2020;42(4). doi:10.1111/ics.12626
9. Roggenkamp D, Sammain A, Fürstenau M, et al. Thiamidol® in moderate-to-severe melasma: 24-week, randomized, double-blind, vehicle-controlled clinical study with subsequent regression phase. *J Dermatol.* 2021;48(12). doi:10.1111/1346-8138.16080
10. Lima PB, Dias JAF, Cassiano DP, et al. Efficacy and safety of topical isobutylamido thiazolyl resorcinol (Thiamidol) vs. 4% hydroquinone cream for facial melasma: an evaluator-blinded, randomized controlled trial. *J Eur Acad Dermatol Venereol.* 2021;35(9). doi:10.1111/jdv.17344
11. Disphanurat W, Srisantithum B. Efficacy and safety of 0.15% isobutylamido thiazolyl resorcinol combined with hyaluronic acid vs 0.15% isobutylamido thiazolyl resorcinol or hyaluronic acid alone in melasma treatment: A randomized evaluator-blind trial. *J Cosmet Dermatol.* 2021;20(11). doi:10.1111/jocd.14031
12. Roggenkamp D, Dlova N, Mann T, et al. Effective reduction of post-inflammatory hyperpigmentation with the tyrosinase inhibitor isobutylamido-thiazolyl-resorcinol (Thiamidol). *Int J Cosmet Sci.* 2021;43(3). doi:10.1111/ics.12694
13. Hornyak TJ. Next time, save mushrooms for the pizza! *J Invest Dermatol.* 2018;138(7). doi:10.1016/j.jid.2018.03.003

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