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The efficacy of cysteamine as a melasma therapy: a systematic review of trial studies

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Abstract

Melasma is a chronic and refractory hyperpigmentation disorder that predominantly affects women and individuals with darker skin tones. Treatment remains challenging due to issues related to efficacy, side effects, and high recurrence rates. Cysteamine is a depigmenting agent that has demonstrated promising outcomes in melasma management with minimal adverse effects. This study evaluates the effectiveness of cysteamine as a treatment for melasma. A systematic review was conducted using databases from PubMed, Google Scholar, and ScienceDirect, including articles published over the past 10 years (2013–2023). Eight studies met the inclusion criteria for this review. Cysteamine showed good therapeutic efficacy, reflected in reductions in the melasma area and severity index (MASI) ranging from 1.5 to 10.07, with a mean decrease of 5.73. No severe adverse effects were reported, and only mild reactions such as erythema, itching, irritation, dry skin, tingling, and burning sensations were noted. Overall, cysteamine is demonstrated to be an effective and safe therapy for melasma, offering satisfactory clinical improvement with minimal side effects.

Keywords: cysteamine, hyperpigmentation, MASI, melasma

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Introduction

Melasma is a chronic and refractory hyperpigmentation disorder that frequently occurs on sun-exposed areas of the skin (1, 2), with the face being the most commonly affected site (3). Its global prevalence is approximately 1%, and it is more frequently seen in women and in individuals with darker skin tones, particularly those with Fitzpatrick skin types III–V, such as populations in Southeast Asia and South America. The peak incidence typically occurs between the second and fourth decades of life (4, 5).

In Southeast Asia, the prevalence of melasma is markedly higher than the global average, reaching 20% in men and 40% in women. In Indonesia specifically, melasma comprises 4% of all dermatological cases and accounts for more than 50% of hyperpigmentation disorders (6, 7).

Melasma is characterized by symmetrical brown to black patches with irregular borders (8). These lesions commonly appear on specific areas of the face, including the forehead, chin, lips, and nose (9). Although the exact etiology of melasma remains unclear, several factors are believed to contribute to its development, such as ultraviolet (UV) radiation, hormonal influences, and genetic predisposition. In some cases, melasma may also occur idiopathically (10, 11).

Given its substantial cosmetic impact and the resulting reduction in quality of life, the management of melasma has been extensively studied in recent years. Despite this, current treatment approaches still present multiple challenges, including limited therapeutic effectiveness, potential side effects, and frequent recurrence after therapy is discontinued (9).

The management of melasma is generally classified into topical therapy, chemical peeling, laser treatment, phototherapy, and systemic therapy (13). Cysteamine is a topical treatment option that exerts its effect by inhibiting tyrosinase activity. Several previous studies have demonstrated the efficacy of cysteamine in treating melasma, reporting satisfactory outcomes with minimal side effects (1).

Although earlier systematic reviews have examined the effectiveness of cysteamine as a therapy for melasma, these reviews have largely focused on the uniformity of cysteamine dosing. Other important aspects, such as treatment duration, Fitzpatrick skin types, and adverse effects, remain insufficiently reported.

Methods

This systematic review study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines through the PubMed, Google Scholar, and Science Direct databases with the help of the Endnote 21 application (Clarivate, Philadelphia, USA). An article search was carried out using the following keywords: ((Melasma) OR (Chloasma)) AND ((Management) OR (Therapy) OR (Treatment)) AND (Cysteamine). The inclusion criteria for articles in this study were an randomized control trial (RCT) or quasi-experimental study using Indonesian or English as the main language, published in the last 10 years from 2013 to 2023 and presenting data such as sample size, demographic data, Fitzpatrick skin type, type of intervention provided, duration of therapy, efficacy, side effects, and recurrence rates. Efficacy was assessed based on the melasma area and severity index (MASI), including the modified MASI (mMASI) and hemi-MASI. Exclusion criteria were articles in languages other than English or Indonesian and non-human studies. Data extracted from the articles consisted of the author's name, year of

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publication, type of study, study location, follow-up time, study subjects, intervention, and study outcome.

Results

Study characteristics

Eighty-two articles were found during the initial search process. Three duplicate articles were excluded. A review of the abstracts excluded 38 articles, resulting in 41 full-text articles assessed for eligibility. From the 41 full-text articles, eight studies were included in this study: two quasi-experimental studies and six RCTs. There were 338 subjects in the eight studies. The subjects' age ranged from 18 to 55 years. The subjects were predominantly women (94.1%). There were three studies from Iran, two studies from Brazil, and one study each from Switzerland, Australia, and Indonesia (Fig. 1).

Main outcome

All studies administered topical cysteamine, predominantly in cream formulations containing 5% cysteamine hydrochloride as the active compound. The vehicle across studies was typically a stabilized cream base designed to minimize cysteamine oxidation and odor, consistent with commercial formulations used in clinical practice. Although the concentration was consistent at 5%, some trials evaluated combination formulations, such as cysteamine 5% with nicotinamide 4% or cysteamine 5% layered with tranexamic acid 3%, whereas others compared cysteamine monotherapy against hydroquinone or the modified Kligman formula. No study reported using gel, lotion, or ointment vehicles. Therefore, all data reflect outcomes from topical 5% cysteamine cream–based preparations, either alone or in combination with adjunct agents, ensuring a high level of formulation consistency across trials. The Fitzpatrick skin types of the subjects were mostly types III and IV in four studies and, type II–V in three studies. The efficacy of cysteamine was assessed based on the change in the MASI score. The change in the MASI score ranged from 1.50 to 10.07 with a mean of 5.73. The lowest change in the MASI score was in the Australian study and the highest change in the Swiss study. In studies with Fitzpatrick skin types III and IV, efficacy was obtained with a range of changes in MASI scores from 5.36 to 10.07 with a mean of 7.91. In contrast, studies with Fitzpatrick II–V skin types had lower efficacy with changes in MASI scores of 1.50–4.00 and a mean of 2.77. One study does not describe the Fitzpatrick skin types of the subjects, reporting changes in the MASI score of 5.29 in the cysteamine group and 2.22 in the control group. The duration of cysteamine therapy ranged from 2 to 4 months (Table 1).

Regarding efficacy assessment, three studies used the MASI score, whereas five studies employed the mMASI score to capture pigmentation changes more precisely. The largest mean reductions were observed in Switzerland (–10.07 MASI) and Iran (–10.0 MASI), both dominated by Fitzpatrick III–IV skin types, whereas smaller changes appeared in Australia (–1.5 mMASI) and Brazil (–2.8 to–4.0 mMASI), which included lighter phototypes and quasi-experimental designs. Iranian head-to-head RCTs showed moderate improvement for cysteamine versus tranexamic acid (–5.36 mMASI vs. –4.91 mMASI) and comparable outcomes versus the modified Kligman formula (–6.21 mMASI vs. –5.59 mMASI). Treatment duration did not demonstrate a linear efficacy trend. A 2-month Indonesian trial (MASI) achieved –5.29, whereas the 3- and 4-month protocols ranged from –1.5 to –10.07. Overall, cysteamine yielded consistent MASI/mMASI improvement with favorable tolerability across regions and study designs.

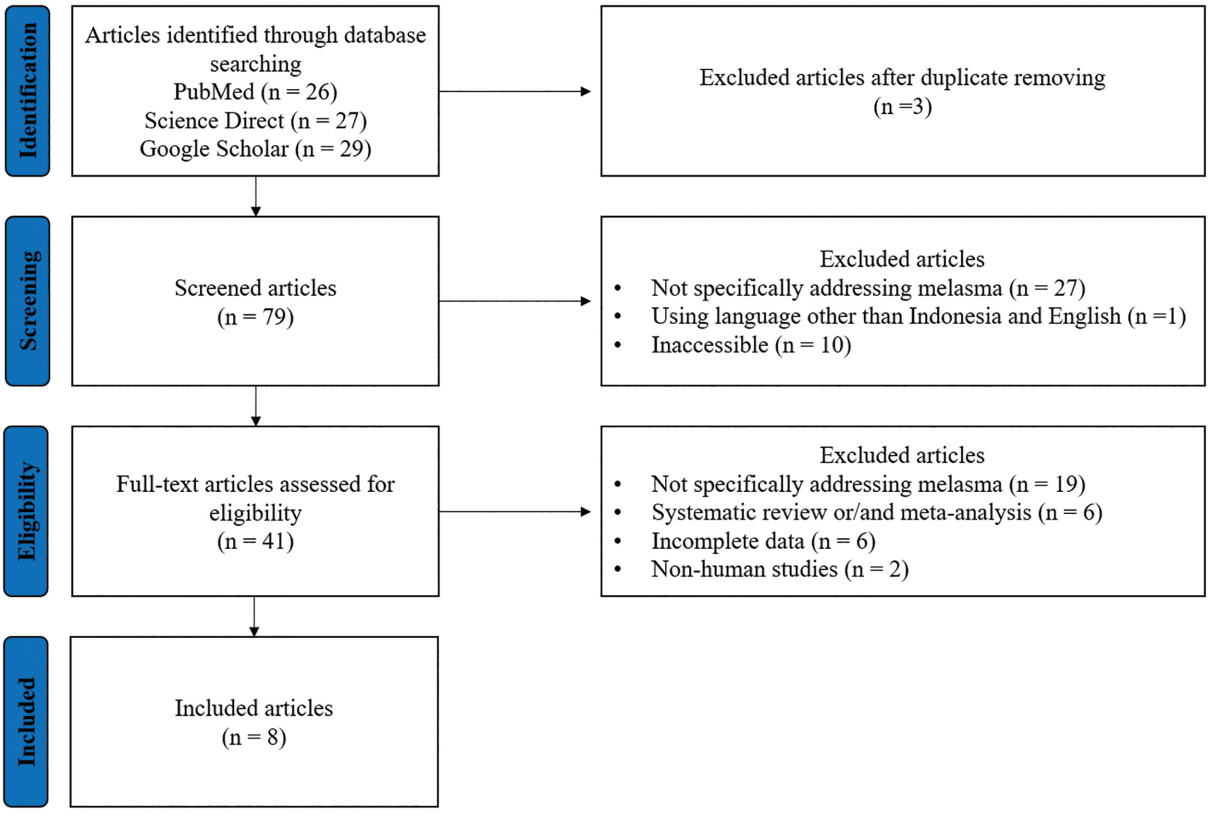

Figure 1 | Article search flowchart.

Table 1 | **Characteristics of the included studies.**

Author	Study location	Subjects	Study design	Fitzpatrick skin type	Intervention	Therapy duration	Efficacy	Side effects
Crocco et al., 2023 (13)	Brazil	53 females 27–50 years old	Quasi-experimental	II–V	Cysteamine 5% combined with nicotinamide 4% without control group	3 months	mMASI 6.7 ± 3.2 at beginning of treatment to 3.9 ± 2.3 at end of treatment (changes: 2.8)	Burning sensation, erythema, itching, desquamation, dry skin, irritation
Farshi et al., 2018 (14)	Switzerland	40 subjects, 6 male and 34 female, 18–50 years old	RCT	III and IV	Cysteamine 5% with placebo control group	4 months	MASI Cysteamine: 18.1 ± 8.1 at start of treatment to 8.03 ± 5.2 at end of treatment (changes: 10.07) Placebo: 13.2 ± 7.4 at start of treatment to 12.2 ± 7.4 at end of treatment (changes: 1.0)	Dispigmentation, irritation, dry skin, burning sensation, itching, erythema
Lima et al., 2020 (15)	Brazil	40 female subjects 30–55 years old	Quasi-experimental	II–V	Cysteamine 5% with 4% hydroquinone comparison group	4 months	mMASI Cysteamine: 9 at startof treatment to 5 at end of treatment (changes: 4) Hydroquinone: 6 at start of treatmen to 2 at end of treatment (changes: 4)	Erythema, burning sensation
Mansouri et al., 2015 (16)	Iran	53 subjects, 7 male and 46 female, 23–50 years old	RCT	III and IV	Cysteamine 5% with placebo control group	4 months	MASI Cysteamine: 17.2 ± 8.3 at start of treatment to 7.2 ± 5.5 at end of treatment (changes: 10) Placebo: 13 ± 8 at start of treatment to 11.6 ± 7.9 at end of treatment (changes: 1.4)	Erythema, itching, burning sensation, dry skin, irritation, hyperpigmentation
Nguyen et al., 2020 (17)	Australia	20 female subjects › 18 years old	RCT	II–V	Cysteamine 5% with 4% hydroquinone comparison group	4 months	mMASI Cysteamine: 7.1 ± 3.4 at start of treatment to 5.6 ± 2.73 at end of treatment (changes: 1.5) Hydroquinone: 9.2 ± 5.7 at start of treatment to 6.29 ± 4.8 at end of treatment (changes: 2.93)	Irritation, erythema, acne vulgaris, burning sensation, itching
Karrabi et al., 2020 (18)	Iran	54 subjects, 5 male and 49 female, 18–50 years old	RCT	III and IV	Cystamine 5% with tranexamic acid comparison group	4 months	mMASI Cysteamine: 11.68 ± 2.70 at start of treatment to 6.32 ± 2.11 at end of treatment (changes: 5.36) Tranexamic acid: 10.43 ± 2.69 at start of treatment to 5.52 ± 2.55 at end of treatment (changes: 4.91)	Erythema, dry skin, itching, burning sensation, irritation
Karrabi et al., 2020 (19)	Iran	50 subjects, 2 male and 48 female, 20–50 years old	RCT	III and IV	Cysteamine 5% with comparison group given modified Kligman formula (hydroquinone 4%, retinoid acid 0.05%, betamethasone 0.1%)	4 months	mMASI Cysteamine: 12.3 at start of treatment to 6.09 at end of treatment (changes: 6.21) Kligman formula: 12.63 at start of treatment to 7.04 at end of treatment (Changes: 5.59)	Erythema, dry skin, itching, burning sensation, irritation
Dewi et al., 2021 (20)	Indonesia	28 female subjects 20–50 years old	RCT	Not described	Combination of cystamine 5% and tranexamic acid 3% with comparison group given Kligman formula (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%)	2 months	MASI Cysteamine and tranexamic acid: 13.18 at start of treatment to 7.89 at end of treatment (changes: 5.29) Kligman formula: 13.33 at start of treatment to 11.11 at end of treatment (changes: 2.22)	Itching, tingling

MASI = melasma area and severity index, mMASI = modified melasma area and severity index, RCT = randomized controlled trial.

Side effects

Across the eight trials, side effects were predominantly mild and localized. Erythema, itching, burning, irritation, and dry skin were most frequent, whereas acne, desquamation, dyspigmentation or hyperpigmentation, and tingling were reported less consistently, with no severe events documented.

Discussion

There is currently no consensus on a gold-standard treatment for melasma, and management continues to be challenging due to the condition's chronicity and high recurrence rate (2, 21). Available therapeutic options are generally categorized into topical agents, chemical peeling agents, laser and phototherapy modalities, and systemic therapies (12). Cysteamine is classified as a topical treatment, with the 5% formulation being one of the most widely used preparations in melasma management (2).

Cysteamine is a natural compound produced through the degradation of L-cysteine and is known for its potent antioxidant properties (22). It is present in mammalian tissues, including in humans, and has been widely recognized for its depigmenting activity (23, 24).

Cysteamine exerts its therapeutic effect through both direct and indirect pathways: directly by inhibiting tyrosinase and peroxidase enzyme activity, and indirectly by functioning as an antioxidant, acting as a chelating agent, and increasing intracellular glutathione levels (25). Tyrosinase and peroxidase are key enzymes required for melanin synthesis. By markedly reducing dopaquinone concentrations, cysteamine disrupts melanogenesis, thereby preventing hyperpigmentation. Furthermore, the glutathione-enhancing effect of cysteamine promotes a shift from eumelanin to pheomelanin synthesis, which slows overall melanin production (13, 26).

The MASI score is a subjective assessment that evaluates the extent of the affected area, the darkness of the lesions, and their homogeneity, resulting in a final score ranging from 0 to 48 (27, 28). Across the studies, reductions in MASI scores ranged from 1.50 to 10.07, with a mean decrease of 5.80. An interesting finding in this study is that cysteamine demonstrated greater efficacy in patients with Fitzpatrick skin types III and IV compared with those classified as Fitzpatrick types II–V. Although the underlying reason for this observation remains unclear, the authors hypothesize that individuals with darker skin types, who have a higher baseline melanin content, may require a smaller absolute reduction in melanin for the affected areas to return to a normal skin tone (29).

The duration of therapy across the studies ranged from 2 to 4 months. Although studies with a 3-month treatment period reported smaller reductions in MASI scores, this cannot be interpreted as a suboptimal duration, given that only one study applied a 3-month regimen and another study with a 4-month duration demonstrated an even smaller MASI improvement. In addition, an Indonesian study with a 2-month treatment period also reported comparatively modest reductions in MASI scores.

There were several limitations of this systematic review. First, not all studies were RCTs. There were two quasi-experimental studies that affected the reliability of the study. Second, the authors limited the language of the articles used to Indonesian and English, and so there may be articles in other languages that reveal the effectiveness of cysteamine as a melasma therapy that are not included.

Conclusions

Cysteamine is a depigmenting agent that has been shown to be effective and safe as a treatment for melasma with minimal side effects. It shows satisfactory results as a melasma therapy, especially in individuals with darker skin tones.

Future studies on cysteamine as a melasma therapy should aim to strengthen the current evidence base through large-scale, multicenter randomized controlled trials with standardized methodologies. Research should focus on evaluating various cysteamine concentrations, formulations, and combination regimens to identify the most effective and tolerable options across different Fitzpatrick skin types. Longer follow-up periods are also needed to assess relapse rates and long-term safety profiles because most current studies have relatively short observation durations. In addition, the inclusion of objective measurement tools such as colorimetric analysis or spectrophotometry could improve the accuracy of treatment efficacy assessment beyond MASI or mMASI scores. Studies exploring the molecular mechanisms of cysteamine's depigmenting action and its interaction with oxidative stress pathways could further clarify its therapeutic potential. Finally, future research should consider patient-reported outcomes and quality-of-life measures to provide a more comprehensive understanding of cysteamine's real-world benefits in melasma management.

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