

The Role of Cysteamine Cream in Hyperpigmentation Disorders: A Review

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ABSTRACT

Hyperpigmentation is a skin pigmentation disorder caused by increased melanin production or deposition. Hydroquinone remains the first-line topical therapy, but long-term use is limited by the risk of side effects. Cysteamine is a multitarget depigmenting agent with potential as an effective and safe alternative therapy. To examine the mechanism of action, effectiveness, safety, and potential use of cysteamine cream in various hyperpigmentation disorders. A literature review of articles from PubMed, NCBI, and Google Scholar published in the last 10 years was conducted. This included randomized controlled trials (RCTs), systematic reviews, and meta-analyses using the keywords cysteamine cream and hyperpigmentation. The literature review showed that cysteamine 5% cream is effective in reducing hyperpigmentation, especially melasma, with comparable effectiveness to hydroquinone 4%. The mechanisms include inhibition of tyrosinase, peroxidase, and melanogenesis, as well as increased antioxidant activity. Reported side effects are generally mild, such as erythema, burning sensation, pruritus, and local irritation, with no risk of toxicity to melanocytes with long-term use. Evidence regarding its effectiveness in post-inflammatory hyperpigmentation (PIH) and other forms of hyperpigmentation is limited. Cysteamine 5% cream is an effective, safe, and potentially effective depigmentation therapy as an alternative to hydroquinone, although further research is needed, particularly in PIH and other forms of hyperpigmentation

INTRODUCTION

Hyperpigmentation is a skin pigmentation disorder characterized by increased melanin production or deposition, resulting in areas of skin that are darker than the surrounding tissue. This condition encompasses various diseases, such as melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, and other forms of hyperpigmentation that can affect all skin types. Hyperpigmentation generally appears in visible areas, especially the face, causing cosmetic problems, decreased self-confidence, and negatively impacting the sufferer's quality of life. Furthermore, the chronic nature of the disease, its recurrence, and its influence on various endogenous and exogenous factors make managing hyperpigmentation disorders challenging in clinical practice.¹

Pathophysiologically, hyperpigmentation occurs due to increased melanocyte activity, leading to excess melanin production. Various factors are known to play a role in this process, including exposure to ultraviolet radiation and visible light, inflammation, hormonal changes, genetic predisposition, and oxidative stress, which affect melanocyte activity and the melanogenesis pathway. Management of hyperpigmentation disorders aims to inhibit melanin formation, accelerate the elimination of established pigment, and prevent recurrence through adequate photoprotection. Current therapeutic approaches include the use of sunscreens, topical agents, systemic therapies, chemical peels, and various light- and laser-based procedures as clinically indicated. Among these options, hydroquinone remains the first-line (gold standard) topical therapy due to its ability to inhibit tyrosinase activity, thereby reducing melanin synthesis. However, the use of hydroquinone has several limitations, particularly with long-term therapy, as it can cause side effects such as skin irritation, contact dermatitis, erythema, and even exogenous ochronosis with prolonged use.¹

One depigmenting agent that can treat skin hyperpigmentation is cysteamine. Cysteamine is an endogenous aminothiols produced by the degradation of L-cysteine. It has strong antioxidant activity and has long been used in the treatment of cystinosis. In dermatology, cysteamine is known to work through various mechanisms, including inhibiting tyrosinase and peroxidase activity, chelating metal ions required for melanogenesis, increasing intracellular glutathione levels, and shifting melanin synthesis from eumelanin to pheomelanin, thus reducing overall skin pigment formation. These multiple mechanisms of action make cysteamine a promising therapeutic candidate for various hyperpigmentation disorders.²

A meta-analysis by Dos Santos-Neto et al. (2022) showed that the use of 5% cysteamine provided significant improvement in melasma severity with a good safety profile and generally mild side effects. These findings were reinforced by a more recent meta-analysis by Wu et al. (2024), which reported that cysteamine was more effective than placebo in reducing hyperpigmentation, while its effectiveness was not significantly different from hydroquinone, the modified Kligman formula, or tranexamic acid mesotherapy. These results indicate that cysteamine has comparable effectiveness to standard therapies that have been used so far.^{3,4} This literature review aims to comprehensively examine

the mechanism of action, clinical effectiveness, safety, and potential use of cysteamine cream as a therapeutic option for hyperpigmentation.

LITERATURE REVIEW

A meta-analysis by Dos Santos-Neto et al. (2022) showed that the use of 5% cysteamine provided significant improvement in melasma severity with a good safety profile and generally mild side effects. These findings were reinforced by a more recent meta-analysis by Wu et al. (2024), which reported that cysteamine was more effective than placebo in reducing hyperpigmentation, while its effectiveness was not significantly different from hydroquinone, the modified Kligman formula, or tranexamic acid mesotherapy. These results indicate that cysteamine has comparable effectiveness to standard therapies that have been used so far.^{3,4} This literature review aims to comprehensively examine the mechanism of action, clinical effectiveness, safety, and potential use of cysteamine cream as a therapeutic option for hyperpigmentation.

METHODOLOGY

This literature review uses methods to analyze articles from databases such as Systematic Literature Reviews, Meta-Analysis, and Randomized Controlled Trials (RCTs). This method collects, identifies, and evaluates articles on a specific topic using the keywords cysteamine cream and hyperpigmentation. Article sources used journal databases such as PubMed, NCB, and Google Scholar, with publication dates spanning the last ten years.

RESEARCH RESULT

Based on a literature review of various scientific publications on cysteamine 5% cream therapy for hyperpigmentation, the focus is on melasma, while evidence for post-inflammatory hyperpigmentation (PIH) and lentigo is still relatively limited. The majority of available studies are randomized controlled trials (RCTs), systematic reviews, and meta-analyses, thus providing a high level of evidence. Overall, all studies demonstrate that cysteamine is an effective depigmenting agent with good safety and comparable efficacy to 4% hydroquinone.

Hyperpigmentation

Hyperpigmentation is a skin pigmentation disorder characterized by increased melanin production or accumulation, causing areas of skin to appear darker than the surrounding skin.⁵ Hyperpigmentation occurs through increased melanocyte activity, increased melanin synthesis, impaired melanosome distribution, or melanin deposition in the epidermis and dermis, influenced by genetic factors, exposure to ultraviolet radiation, inflammation, hormonal changes, medications, and the aging process.⁵ In addition to causing cosmetic problems, hyperpigmentation can have significant psychological impacts, such as decreased self-confidence and quality of life, making it a frequent reason for patients to seek dermatological treatment.⁶

Hyperpigmentation can be classified based on the location of melanin deposition into epidermal, dermal, and mixed hyperpigmentation, each of which

has a different clinical presentation, prognosis, and therapeutic response.⁵ Based on its etiology, hyperpigmentation is divided into melasma, post-inflammatory hyperpigmentation, lentigo solaris, drug-induced hyperpigmentation, and hyperpigmentation associated with systemic diseases such as Addison's disease and hemochromatosis.⁵ Classifying hyperpigmentation is crucial because each type has a distinct pathogenesis mechanism, requiring a therapeutic approach tailored to the underlying cause.⁶

Melasma is a form of acquired hyperpigmentation characterized by symmetrical hyperpigmented macules or patches on the face, particularly areas frequently exposed to sunlight. Its pathogenesis involves exposure to ultraviolet radiation, hormonal factors, genetic predisposition, and oxidative stress.⁶ Post-inflammatory hyperpigmentation occurs after inflammatory processes or skin injuries, such as acne, dermatitis, burns, or dermatological procedures, due to increased melanin synthesis and deposition during tissue healing.⁵ Meanwhile, lentigo solaris develops as a result of chronic ultraviolet light exposure, which leads to increased melanocyte activity and melanin accumulation. Hyperpigmentation due to drugs or systemic diseases occurs through disruption of melanogenesis regulation or pigment deposition triggered by medications or metabolic and endocrine disorders.^{5,6}

Cysteamine

Cysteamine is an endogenous aminothiols compound produced by coenzyme A metabolism. It acts as a depigmenting agent by inhibiting tyrosinase enzyme activity, reducing dopaquinone formation, and by acting as an antioxidant that reduces melanin formation in the skin.⁷ Cysteamine is widely used as a topical therapy for various hyperpigmentation disorders, such as melasma, post-inflammatory hyperpigmentation, and solar lentigines, due to its high efficacy and lower risk of side effects compared to hydroquinone during long-term use.⁸

Various concentrations of cysteamine have been developed to increase therapeutic effectiveness while maintaining skin tolerability.⁷ Formulations containing 1% cysteamine are generally used as part of a combination with other depigmenting agents, such as niacinamide, tranexamate, and Galactomyces ferment filtrate, which have been reported to improve mild to moderate hyperpigmentation.⁹ However, because it is used in combination formulations, the contribution of 1% cysteamine as a single ingredient to the depigmenting effect has not been determined.⁹

A concentration of 2.5% cysteamine has also been developed in cosmetic formulations to enhance skin lightening effects.⁹ Research shows that formulations containing 2.5% cysteamine can reduce the melanin index and improve skin radiance when combined with other active ingredients.⁹ However, to date, there are no randomized clinical trials evaluating the effectiveness of 2.5% cysteamine as monotherapy compared to higher concentrations.⁷ Therefore, scientific evidence regarding the effectiveness of 2.5% cysteamine is still more limited than that of 5%.⁸

Among all available concentrations, 5% cysteamine has the strongest scientific evidence for treating hyperpigmentation.⁷ Several randomized,

double-blind, controlled trials have shown that 5% cysteamine significantly reduces Melasma Area and Severity Index (MASI) scores and improves hyperpigmentation with comparable effectiveness to hydroquinone.¹⁰ The use of 5% cysteamine generally causes only mild side effects, such as erythema, burning sensation, pruritus, and transient irritation, which are well tolerated by most patients.⁸ A recent meta-analysis also concluded that 5% cysteamine is effective and safe for melasma treatment based on available clinical evidence.⁷ To date, 5% cysteamine remains the concentration with the highest level of evidence, while 1% and 2.5% still require further clinical research to ensure their long-term effectiveness and safety.^{7,8}

Table 1. Summary of Main Research on Cysteamine Cream

Author	Year	Design	Sample	Results
Daniel <i>et al.</i> ¹¹	2022	<i>Prospective open intervention pilot study</i>	10 women with melasma aged 40- 58 years	13.5% decrease in mMASI score 50% of patients showed clinical improvement based on GAIS No significant improvement in quality of life Mild side effects
Agenor <i>et al.</i> ⁸	2022	<i>Systematic review dan meta-analysis</i>	6 RCT study	Cysteamine 5% significantly reduced melasma hyperpigmentation. Its effectiveness was comparable to or better than several comparator therapies (hydroquinone, placebo, and tranexamic acid). Minor side effects
Behrooz <i>et al.</i> ¹⁰	2018	<i>Case report</i>	A 44-year-old woman with melasma resistant to Kligman's formula	The MASI score decreased from 12 to 1.4 after 2 months of therapy. After 4 months, hyperpigmentation, erythema, and telangiectasia significantly improved. No recurrences or side effects were observed during the 3- year follow-up.

Author	Year	Design	Sample	Results
Paula <i>et al.</i> ¹²	2020	<i>Quasi-randomized, multicenter, parallel, evaluator-blinded clinical trial</i>	40 women with melasma	A 38% decrease in mMASI on day 120 in the cysteamine group Both groups showed up to 74% aesthetic improvement based on GAIS No serious side effects were observed
Nomathamsanqa <i>et al.</i> ¹³	2020	<i>Case Report</i>	A 20-year-old woman with Fitzpatrick Skin Type V who experienced chronic PIH	PIH improved significantly after using 5% cysteamine. Melanin index decreased from 904 to 818. No side effects were observed during therapy. Cysteamine was well tolerated.
Jennifer <i>et al.</i> ¹⁴	2020	<i>Double-blind RCT</i>	20 women with melasma	21.3% decrease in mMASI in the cysteamine group mild and reversible side effects
Najmeh <i>et al.</i> ¹⁵	2021	<i>Systematic Review</i>	8 study	Cysteamine 5% provides significant improvements in MASI/mMASI scores, melanin content, and patient satisfaction. Its effectiveness is equivalent to hydroquinone. Reported side effects are generally mild.

Effectiveness of Cysteamine on Melasma

Melasma is the most widely studied hyperpigmentation disorder for which topical cysteamine is used. Many studies report a reduction in the Melasma Area and Severity Index (MASI) and modified MASI (mMASI) after 12–16 weeks of 5% cysteamine.⁸

A recent meta-analysis in 2024 showed that cysteamine provided significantly better improvement than placebo, with a standardized mean difference (SMD) of -0.84. However, when compared with 4% hydroquinone, no

significant difference in effectiveness was found, indicating that both therapies have relatively equivalent depigmentation capabilities.⁸

Other studies have also shown that most patients begin to experience clinical improvement by week 8, with optimal results after week 16. In addition to a decrease in MASI scores, most patients also reported an improved quality of life due to a reduction in facial hyperpigmentation lesions.⁷

Effectiveness in Post-Inflammatory Hyperpigmentation (PIH)

The number of studies on the use of cysteamine in PIH is still fewer than in melasma. However, several studies report that cysteamine's antioxidant and tyrosinase-inhibiting mechanisms have the potential to accelerate the resolution of PIH, particularly those caused by acne, laser procedures, or other skin inflammation.¹⁶

This effectiveness is thought to be related to cysteamine's ability to suppress eumelanin formation and reduce oxidative stress, which plays a key role in post-inflammatory hyperpigmentation. Therefore, cysteamine is beginning to be considered as a non-hydroquinone alternative in patients with chronic PIH, particularly in individuals with darker skin phototypes.¹⁶

Mechanism of Action of Cysteamine

Cysteamine is a natural aminothiols produced by coenzyme A metabolism and has various depigmentation mechanisms. Unlike hydroquinone, which works primarily through tyrosinase inhibition, cysteamine acts simultaneously on multiple melanogenesis pathways.¹⁶

These mechanisms include inhibition of tyrosinase activity, inhibition of peroxidase, inhibition of dopaquinone formation, decreased eumelanin synthesis, antioxidant activity that reduces reactive oxygen species (ROS), and chelation of metal ions necessary for melanogenesis.¹⁶

Because it works on multiple biological targets simultaneously, cysteamine is considered to have a lower risk of therapy resistance than other single depigmenting agents.⁷

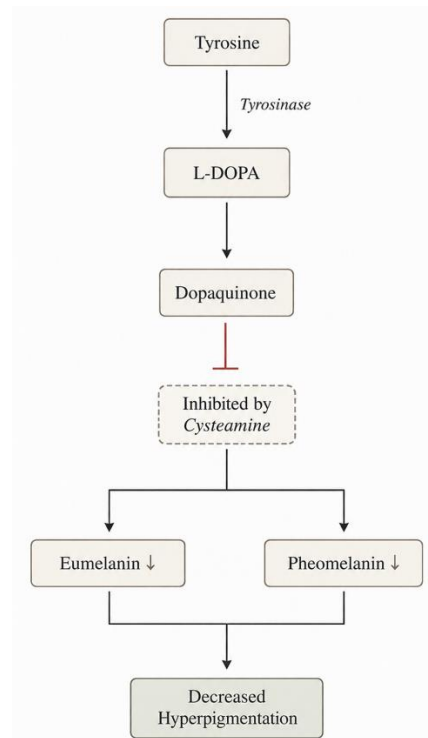


Figure 1. The mechanism of action of cysteamine in the melanogenesis process

Comparison with Other Depigmenting Agents

Hydroquinone remains the gold standard for melasma therapy. However, long-term use of hydroquinone can cause chronic irritation, rebound pigmentation, and exogenous ochronosis, so its use is generally limited. In contrast, cysteamine demonstrates relatively equivalent efficacy with no evidence of melanocyte toxicity with long-term use.⁸

In addition to comparisons with hydroquinone, several studies have also evaluated cysteamine against a modified Kligman's formula. The results showed no significant difference in MASI score reduction, suggesting that cysteamine could be an alternative for patients who cannot tolerate hydroquinone.¹⁶

Table 2. Comparison of Cysteamine with Other Depigmenting Agents

Agent	Mechanism	Effectivity	Side Effect
<i>Hydroquinone</i>	Inhibisi tirosinase	Very good	Ochronosis, irritation
<i>Azelaic acid</i>	Inhibisi tirosinase	Moderate	Mild irritation
<i>Kojic acid</i>	Chelating copper	Moderate	Contact dermatitis
<i>Tranexamic acid</i>	Antiangiogenesis	Good	Relatively safe
<i>Cysteamine</i>	Multi-target melanogenesis+ antioksidan	Good-very good	Mild erythema, sulfur odor

Safety of Use

The majority of studies report that cysteamine side effects are mild and transient. The most common complaints include a mild burning sensation, erythema, pruritus, dry skin, and local irritation at the beginning of therapy. Most of these side effects resolve after a few weeks of use without requiring discontinuation of therapy.⁸

One of the main limitations of cysteamine is its strong sulfurous odor, which can decrease patient compliance. However, newer formulations have been developed with improved stability and less odor than earlier formulations.

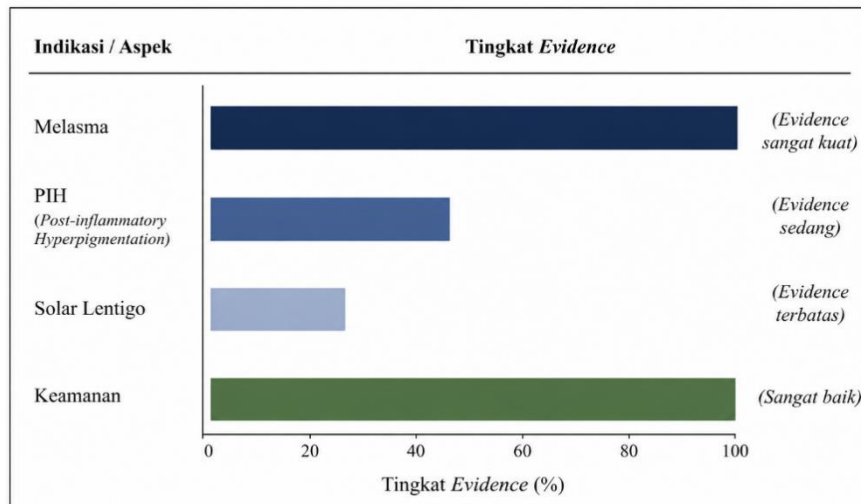


Figure 2. Evidence graph of the use of cysteamine in hyperpigmentation

The Role of Cysteamine as a New Therapy for Hyperpigmentation Disorders

Hyperpigmentation disorders, such as melasma, post-inflammatory hyperpigmentation (PIH), and solar lentigines, are common dermatological problems that significantly impact patients' quality of life. Although not life-threatening, persistent skin discoloration can cause psychosocial distress, lower self-confidence, and impact social interactions. Therefore, effective and safe therapies are a crucial need in clinical practice.⁶

For decades, hydroquinone has been considered the gold standard topical therapy for hyperpigmentation. However, long-term use of hydroquinone is limited by the risks of irritation, contact dermatitis, hypopigmentation, and exogenous ochronosis, prompting the development of new depigmenting agents with similar efficacy but a better safety profile. In this context, cysteamine 5% cream has emerged as one of the most promising alternatives based on various clinical trials and recent meta-analyses.⁶

Biological Mechanisms of Cysteamine in Inhibiting Melanogenesis

The effectiveness of cysteamine stems not only from tyrosinase inhibition but also from biological mechanisms acting at various stages of melanin formation. Cysteamine is an endogenous aminothiols produced by coenzyme A metabolism. It has strong antioxidant activity, thus reducing oxidative stress, which plays a crucial role in melanocyte activation. Furthermore, cysteamine inhibits tyrosinase and peroxidase activity, reduces the conversion of tyrosine to

dopaquinone, increases intracellular glutathione levels, and shifts melanin synthesis from eumelanin to the lighter-colored pheomelanin. The combination of these mechanisms results in a more comprehensive reduction in melanin production than depigmenting agents that work through only one pathway.⁶

Physiologically, oxidative stress is a major factor that increases tyrosinase expression through activation of the microphthalmia-associated transcription factor (MITF) pathway. By reducing reactive oxygen species (ROS) levels, cysteamine not only inhibits melanin formation but also reduces the chronic inflammatory process that contributes to recurrent hyperpigmentation, particularly in melasma and PIH. This explains why clinical improvements achieved through cysteamine therapy tend to be more stable when accompanied by adequate photoprotection.⁶

Clinical Effectiveness in Melasma

Melasma is the indication for which there is the strongest scientific evidence for the use of cysteamine. A recent meta-analysis including seven to eight randomized clinical trials showed that the use of 5% cysteamine for 12–16 weeks resulted in a significant reduction in both MASI and mMASI scores compared to placebo. However, when compared with 4% hydroquinone, the modified Kligman formula, or tranexamic acid mesotherapy, no significant differences in effectiveness were found. In other words, cysteamine provides clinical results equivalent to standard therapies that have been used for many years.⁸

Interestingly, further analysis showed that patients with shorter melasma duration experienced a better response to therapy than those with long-standing disease. This indicates that early intervention may be more effective before chronic dermal changes and deeper melanin deposition occur.⁷

Role in Post-Inflammatory Hyperpigmentation

Although scientific evidence for PIH is more limited than for melasma, cysteamine's mechanism of action provides a strong biological basis for its use in this condition. PIH occurs due to increased melanocyte activity following inflammation, so tyrosinase inhibition and reduced oxidative stress through cysteamine are thought to accelerate pigmentation resolution. Several preliminary studies have shown clinical improvement, particularly in PIH due to acne, laser procedures, and inflammatory dermatitis, although larger clinical trials are needed.⁶

Safety of Use

One of the main advantages of cysteamine over hydroquinone is its safety profile. Meta-analyses indicate that the most common side effects are mild burning, erythema, pruritus, dry skin, and transient irritation. The incidence of these side effects is higher than placebo, but not significantly different from hydroquinone. Most complaints are mild and do not lead to discontinuation of therapy.⁸

Another limitation is the distinctive sulfurous odor due to cysteamine's chemical structure. This odor can decrease patient compliance, especially with

long-term use. However, advances in formulation technology have resulted in more stable cysteamine preparations with a much less pronounced odor.

Table 3. Comparison of topical therapies for hyperpigmentation

Therapy	Mechanism	Effectivity	Advantages	Limitation
Hydroquinone 4%	Inhibisi tirosinase	Very potent	Gold standard	Risk of ochronosis and irritation
Cysteamine 5%	Multi-target melanogenesis + antioksidan	Potent	Safe for longer use	Sulfur odor, mild irritation
Azelaic acid	Inhibisi tirosinase	Moderate	Safe in certain pregnancies according to clinical assessment	Slower response
Kojic acid	Chelating ion tembaga	Moderate	Combination with other agents	Contact dermatitis
Tranexamic acid topikal	Menurunkan aktivasi plasmin	Potent	Effective as an adjunctive therapy	Topical evidence is still developing

DISCUSSION

Overall, several studies indicate that cysteamine 5% cream is an effective and safe depigmentation therapy, especially for melasma. Its effectiveness has been shown to be equivalent to that of hydroquinone 4%, but it has the advantages of a more complex mechanism of action, non-toxicity to melanocytes, and potential for long-term use. Scientific evidence regarding its use in PIH and other forms of hyperpigmentation is still developing, so multicenter studies with larger sample sizes, longer follow-up durations, and evaluation of recurrence rates after discontinuation of therapy are needed.

CONCLUSION AND RECOMMENDATION

Cysteamine 5% cream demonstrates clinical efficacy equivalent to the gold standard hydroquinone, with the advantages of a biological mechanism of action that acts on the melanogenesis pathway and potent antioxidant properties. Cysteamine is non-toxic to melanocytes and does not carry the risk of exogenous ochronosis, adding to its long-term safety.

Side effects of cysteamine are mild and well-tolerated, although the sulfurous odor remains a challenge for patient compliance. The success of cysteamine therapy still depends on adherence and sunscreen use. Further research with larger sample sizes and longer durations is needed to evaluate its effectiveness on post-inflammatory hyperpigmentation (PIH), solar lentigines, and recurrence after discontinuing therapy.

LIMITATION

Based on the literature review, there are several limitations regarding the use of cysteamine cream. Larger studies are needed to strengthen the evidence base, along with long-term evaluation data to evaluate recurrence rates and long-term follow-up. Furthermore, research and clinical trials are very limited in melasma therapy; research is needed to investigate the effectiveness of cysteamine use on other forms of hyperpigmentation.

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