RESEARCH PAPER

Effectiveness of Topical N-Acetyl Glucosamine in Reducing Hyperpigmentation in Patients with Melasma: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Melasma is symmetric facial hyperpigmentation caused by sun exposure. Treatment aims to reduce hypermelanosis without hypopigmentation or irritation. N-acetyl glucosamine (NAG) is an alternative. Studies show topical NAG, alone or combined, reduces hyperpigmentation with a safety profile. This study evaluated evidence for NAG in managing melasma.

Methods: Searches were performed through PubMed, Science Direct, Cochrane, and Google Scholar. Eligible studies included observational studies, RCTs, and trials from the last 25 years (2000–2025) assessing NAG effectiveness in melasma management. Meta-analysis used RevMan 5.4.1. Standardized Mean Difference (SMD) or Mean Difference (MD) with 95% confidence interval (CI) was used for MASI scores. ROB2 or ROBINS-I assessed bias; SIGN evaluated quality.

Results: Of the 7 studies (222 subjects), only 4 were included in the meta-analysis (122 subjects). The use of N-acetyl glucosamine (NAG), either as monotherapy or in combination with other agents, and the Neoretin Discrom Control-based preparation containing NAG, were said to be effective in melasma patients, as shown by decreased in MASI scores in each study. From meta-analysis, combination therapy with N-acetylglucosamine (NAG) did not significantly reduce hyperpigmentation (SMD –1.14; 95% CI –2.82 to 0.54; p=0.18). In contrast, Neoretin Discrom products showed a significant reduction in MASI scores (SMD –2.41; 95% CI –3.86 to –0.97; p=0.001).

Conclusion: NAG may be considered a safe and effective alternative for reducing hyperpigmentation in melasma, either as monotherapy or in combination with other depigmenting regimens.

Keywords: N-acetyl glucosamine, melasma, effectiveness, hyperpigmentation

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INTRODUCTION

Melasma or chloasma is a disorder characterized by symmetric hyperpigmented patches with well-defined borders that generally appear on sun-exposed areas of the face. The most frequent location is the central facial region, found in around 50–80% of cases, although malar and mandibular regions can also be affected [1–4]. Prevalence varies significantly across populations and ethnicities, approximately 1% in the general population but up to 9–50% among high-risk groups, particularly women with darker skin (Fitzpatrick types III–IV) in their third to fourth decades of life [1–4]. Higher incidences have been reported in Middle Eastern, Southeast Asian, Hispanic-American, Mediterranean African, and Brazilian populations. Melasma occurs far more frequently in women, with a 9–10 times higher risk compared to men [5–7].

The exact mechanism of melasma development remains unclear, but contributing factors include: chronic ultraviolet (UV) radiation exposure, hormonal influences (such as pregnancy or oral contraceptives), and genetic predisposition [2,5]. Among these, UV radiation plays a central role, triggering reactive oxygen species (ROS) formation, which accelerates melanogenesis and worsens pigmentation [8].

The primary goal of melasma therapy is to reduce hypermelanosis without causing hypopigmentation or irritation to the surrounding skin. Various treatment modalities are available, yet many carry significant side

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effects. Therefore, natural brightening agents have become an alternative option, including glucosamine. Glucosamine, an amino-monosaccharide naturally present in human tissues, is produced through the amination of glucose, followed by acetylation to form N-acetylglucosamine (NAG). This derivative compound exhibits skin-lightening effects in hypermelanosis by inhibiting tyrosinase glycosylation, thereby reducing melanin production in melanocytes [9].

Several clinical studies have demonstrated that topical NAG, either as monotherapy or in combination (e.g., with niacinamide), reduces skin hyperpigmentation without notable irritation. However, clinical evidence on topical NAG's effectiveness in melasma patients remains limited and fragmented across small-sample studies with varying designs. No consistent conclusion has been reached on the magnitude of NAG's benefit relative to standard therapies. Therefore, this systematic review and meta-analysis (SRMA) aims to consolidate, analyze, and synthesize clinical evidence on the effectiveness of topical N-acetyl glucosamine in reducing hyperpigmentation among patients with melasma.

METHODS

Searching strategy and eligibility criteria

The literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was conducted through the PubMed, Science Direct, Cochrane, and Google Scholar databases. The search terms used included: (n acetylglucosamine OR glucosamine OR acetylglucosamine OR neoretin discrom) AND (melasma OR chloasma) AND (hyperpigmentation OR melanin index OR MASI score). Articles retrieved from these databases were screened based on inclusion and exclusion criteria. Inclusion criteria consisted of: (1) Studies discussing the use of N-acetylglucosamine or cosmetic products containing N-acetylglucosamine in melasma; (2) Human studies involving melasma patients; (3) RCTs, observational studies, or clinical trials; (4) Published within the last 25 years (2000–2025); (5) Published in peer-reviewed journals with full text available; (6) Written in English or Indonesian.

Exclusion criteria included: Non-human studies, case reports or case series, literature reviews, meta-analyses, systematic or narrative reviews, expert opinions, and evidence summaries (e.g., guideline summaries, clinical practice summaries, or consensus statements), as well as full-text articles that were inaccessible.

Study selection and data extraction

To exclude irrelevant studies, two reviewers independently screened the titles and abstracts of the articles, followed by full-text assessments of potentially relevant papers. Both reviewers independently extracted data using a standardized data extraction spreadsheet. Data collected from each eligible publication (where available) included: author, year of publication, inclusion criteria, number of subjects, age, gender, type of melasma, and evaluated outcomes.

Risk of bias and quality of evidence assessment

Risk of bias assessment was carried out using the Cochrane Risk of Bias 2 (RoB2) tool for randomized controlled trials (RCTs) and the ROBINS-I tool for non-RCTs to evaluate the quality of studies included in the quantitative analysis. The overall risk of bias for each study was categorized as low, moderate, or high, and when the available information was insufficient, the bias risk was labeled as "No information."

Quality assessment was also performed independently by two reviewers using the Scottish Intercollegiate Guidelines Network (SIGN) criteria. Any discrepancies between reviewers were resolved through discussion with a third reviewer. The SIGN checklist provides a comprehensive framework for evaluating both RCTs and non-RCTs, focusing on three main aspects: internal validity, overall assessment, and description. The overall quality of each article was then classified as follows: 1+ for meta-analyses, systematic reviews, or RCTs with a low risk of bias; 1- for those with a high risk of bias; 2+ for well-conducted case-control or cohort studies with a low risk of bias; and 2- for case-control or cohort studies with a high risk of bias.

Data synthesis and statistical analysis

All statistical analyses in the meta-analysis were performed using RevMan version 5.4.1. The outcome measures used were Mean Difference (MD) or Standardized Mean Difference (SMD) with a 95% Confidence Interval (CI) for the MASI score, which served as the parameter for hyperpigmentation. Heterogeneity among studies was assessed using the I^2 index, where significant heterogeneity was indicated by $p < 0.10$, and an I^2 value greater than 50% denoted substantial heterogeneity. Small-study effects or publication bias were evaluated using a funnel plot, while subgroup analyses were considered statistically significant when $p < 0.05$.

RESULTS

Characteristics of included studies

The primary literature search identified 6 articles from PubMed, 3 articles from CENTRAL/Cochrane, 78 articles from Science Direct, and 277 articles from Google Scholar, resulting in a total of 364 articles (Figure 1). Screening was conducted to remove duplicates and to evaluate titles and abstracts, yielding 32 articles for further review. After applying the inclusion and exclusion criteria through full-text assessment, 21 articles were excluded for not meeting the inclusion criteria, and 4 articles were excluded because they were not written in English or Indonesian. Consequently, 7 articles with a total of 222 participants were included in the systematic review, but only 4 articles were eligible for inclusion in the meta-analysis (Table 1).

All included studies were published between 2000 and 2025 and consisted of observational studies, randomized controlled trials (RCTs), and clinical studies. All selected studies discussed the effectiveness of N-acetyl glucosamine (NAG) (1 study), NAG combination (2 studies), and topical NAG-containing neoretin products (4 studies) in the management of reducing hyperpigmentation (as seen from the MASI score) in melasma patients.

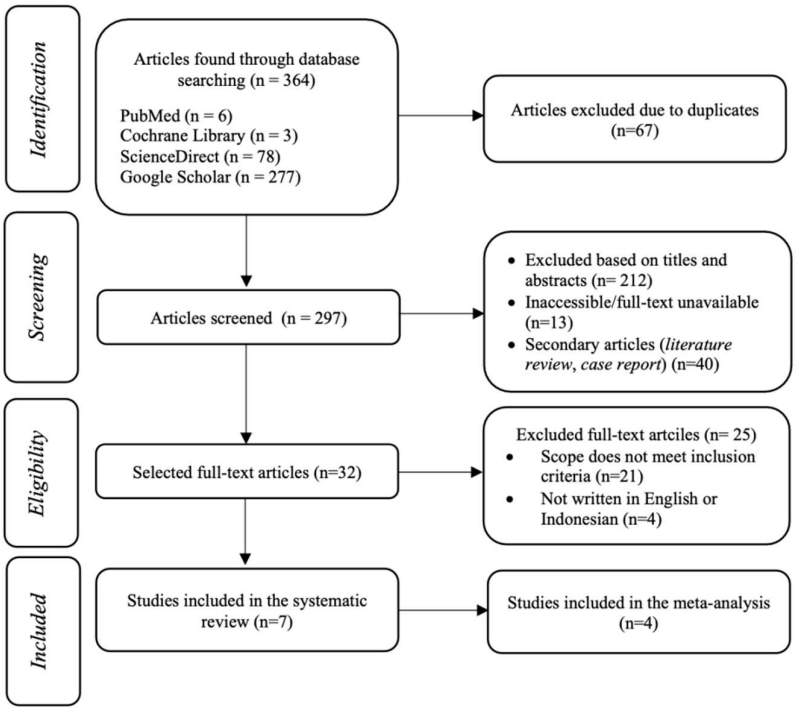

Figure 1. PRISMA Flowchart.

Table 1. Characteristics of included studies.

Author, year	Design	Study quality *	No. of subjects	Age (average)	Ratio (Male: Female)	Melasma type	Country	Type, dosage of NAG, duration	Outcome
Iraji et al, 2009[10]	Randomized controlled trial	1+	30 female patients, aged 20-50 years with symmetrical facial melasma	34,1	0:30	Epidermal, mixed types of melasma	Iran	Cream, 4% NAG, 12 weeks	MASI Score
Manfreda et al, 2023[11]	prospective, randomized, single-blind, study	1+	26 patients with facial melasma	41,5±9,36	1:23	Facial melalsma (types not reported)	Italy	Cream, not reported, 12 weeks	MASI Score
Bissett et al, 2007[12]	Randomized controlled trial	1-	50 Japanese patients with facial hyperpig	Not reported	0:50	Facial melasma	America	Cream, 2% NAG, 8 weeks	Hyper-pigmentation appearance

			mentation (melasma) and 25 Caucasion with melasma						
Luong et al, 2022[13]	clinical trial	2+	36 patients with melasma	45,3 ± 6,3	1:35	Epidermal, mixed types of melasma	Vietnam	Serum, 2% NAG, 4 months	MASI Score
Millan et al, 2016[14]	Prospective, observational open study	2+	30 patients with melasma	52,9	3:27	Facial melasma	Spain	Serum, not reported, 3 months	Change in MASI score (%)
Catala et al, 2023[15]	single-blind, prospective, single-center study	2+	20 patients with facial melasma	42,3	0:20	Facial melasma	Spain	Serum, not reported, 3 months	Change in MASI score (%)
Truchuelo et al, 2014[16]	Randomized controlled trial	1+	30 patients with melasma	39	1:27	Facial melasma	Spain	Gelcream, not reported, 3 months	MASI Score

***based on Scottish Intercollegiate Guidelines Network (SIGN).**

Risk of bias assessment and funnel plots

The risk of bias assessment for each RCT is summarized in Figure 2. Overall, we rated the risk of bias as low in two studies and unclear in two studies. The assessment of risk of bias in non-RCT studies is summarized in Figure 3. Overall, we assess the risk of bias as low in one study and unclear in two studies.

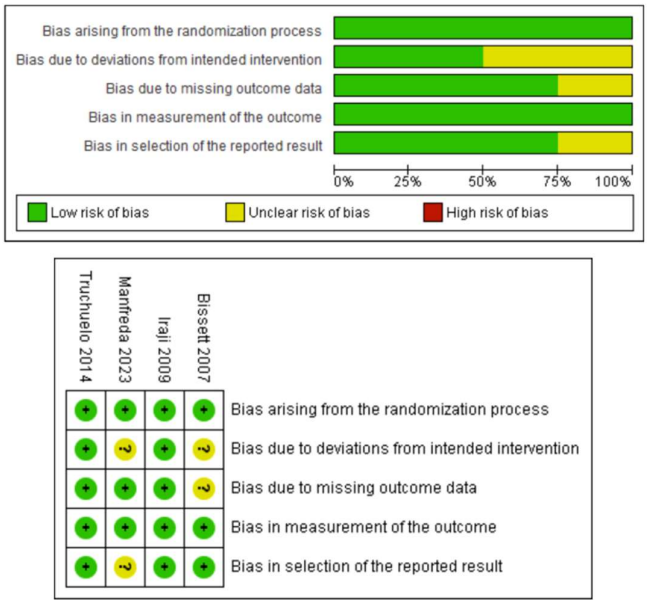

Figure 2. Risk of bias assessment with RoB-2.

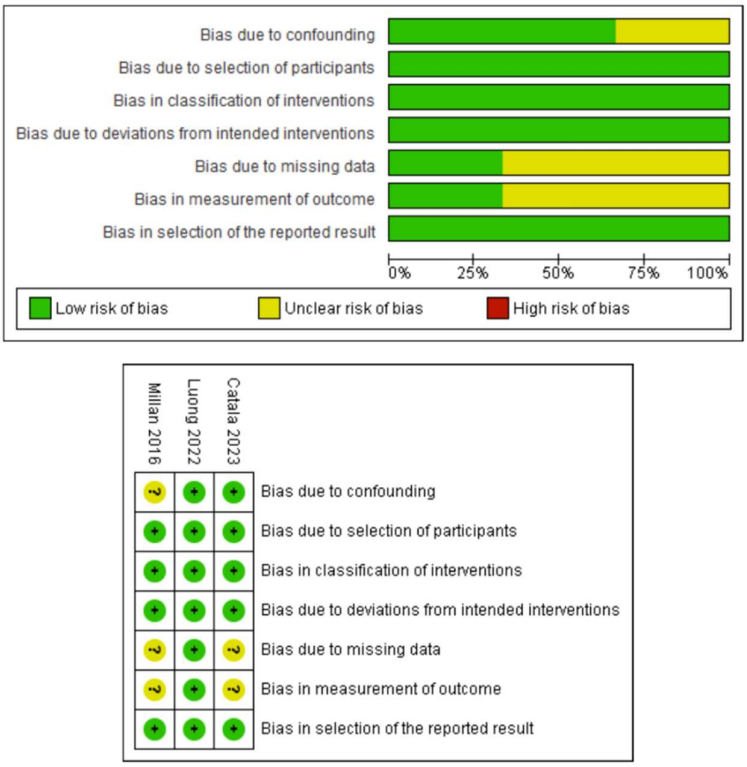

Figure 3. Risk of bias assessment with RoB-2.

The funnel plot included in the meta-analysis is presented in Figure 4. The analysis shows a relatively symmetrical distribution of studies, indicating a low likelihood of publication bias.

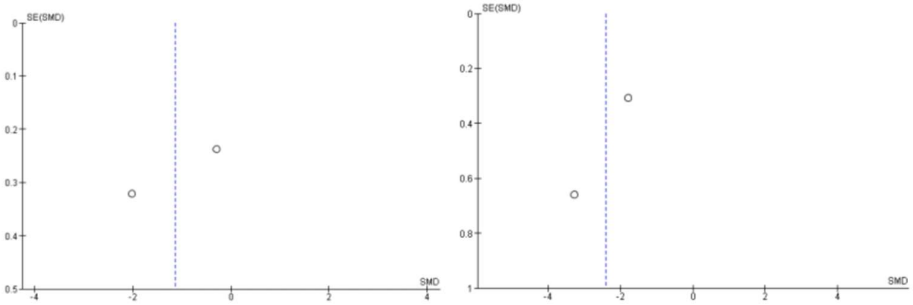

Figure 4. Funnel plots from the meta-analysis of the effectiveness (MASI Score) of NAG in melasma.

Summary of findings

We present a detailed summary of the results from all studies included in this review in the summary table below (Table 2).

Table 2. Summary of study findings on the use of N-acetyl glucosamine in melasma based on the PRISMA methodology.

Reference (author, year)	Location	Results
Iraji et al, 2009[10]	Iran	No significant difference was found in the change or mean value of the Modified MASI score between the two groups after treatment (p = 0.67 and 0.78). However, in the group receiving a combination of N-acetyl glucosamine and nicotinamide, improvement was observed, with the MASI score decreasing from 6.38 ± 2.73 to 1.97 ± 1.39.
Manfreda et al, 2023[11]	Italy	Group A, which received politranexamide, and Group B, which received a combination of N-acetyl glucosamine, ethyl linoleate, and phenyl ethyl resorcinol, both showed a reduction in MASI scores from baseline to week 12. In Group A, the mean MASI score

		decreased from 10.9 ± 7.00 at baseline to 7.75 ± 5.22 at week 12, while in Group B, it decreased from 9.34 ± 6.29 to 7.61 ± 5.24.
Bissett et al, 2007[12]	USA	Topical application of 2% N-acetyl glucosamine (NAG) was shown to reduce the appearance of facial hyperpigmentation. In a second clinical trial combining 2% NAG with 4% niacinamide, an agent previously proven to be clinically active, a greater depigmenting effect was observed. Both agents were well tolerated by the skin.
Luong et al, 2022[13]	Vietnam	Treatment of melasma using Neoretin Discrom Control Serum (containing N-acetyl glucosamine) resulted in a 64% reduction in MASI (from 15.23 ± 3.8 to 5.52 ± 1.4) after 4 months of therapy. The melanin index, measured using a Mexameter, also decreased by 30.4% after 4 months. These findings indicate that Neoretin Discrom Control Serum containing N-acetyl glucosamine is effective and safe for melasma treatment.
Millan et al, 2016[14]	Spain	After treatment with Neoretin® Discrom Control Serum (containing N-acetyl glucosamine), a significant decrease in MASI score was detected, with an average 50% reduction ($p < 0.0001$), and more than 65% of patients showed clinical improvement ($p < 0.0001$). Additionally, 77% of patients reported increased skin brightness.
Catala et al, 2023[15]	Spain	The MASI score significantly decreased at all study visits, with improvement in melasma area and severity observed as early as day 30, and a 48% reduction achieved by the end of treatment. The regimen using Neoretin® Discrom Control Ultra Emulsion and Transition Cream (containing N-acetyl glucosamine) demonstrated effective pigment-correcting activity, significantly improving MASI scores.
Truchuelo et al, 2014[16]	Spain	A significant 70% improvement in MASI after 3 months of treatment was observed on the side treated with Neoretin Discrom Control Gel Cream (containing N-acetyl glucosamine), with MASI decreasing from 9.4 ± 4.6 to 2.4 ± 3. This improvement was comparable to that achieved with hydroquinone. The new combination of retinoids and depigmenting agents (including N-acetyl glucosamine) proved to be both effective and safe in the treatment of melasma.

Effectiveness of NAG (combination and neoretin product containing NAG) in melasma: measured with MASI score as the parameter of hyperpigmentation

Figure 5 illustrates the comparison of effectiveness (MASI scores) from a total of 2 studies. The results of each study regarding the effectiveness of N-acetyl glucosamine (NAG) in reducing MASI scores are summarized in Table 2 above. The meta-analysis revealed that use of NAG in combination, not significantly reduced hyperpigmentation, as stated in not significantly decreased MASI scores, with a pooled standardized mean difference (SMD) of -1.14 (95% CI: -2.82 to 0.54; p=0.18; I^2 = 95%).

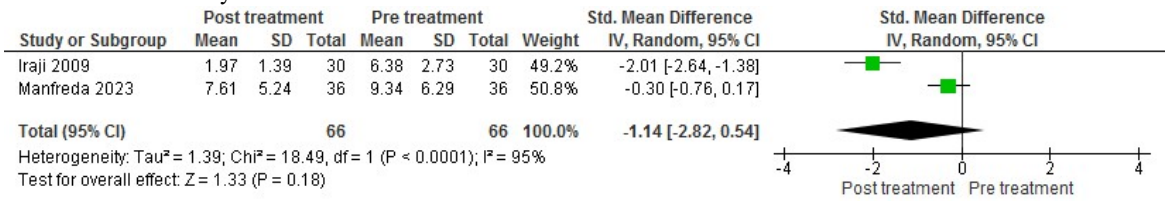

Figure 5. Analysis of MASI score changes as a parameter of hyperpigmentation after treatment with NAG in combination in melasma patients.

Figure 6 illustrates the comparison of effectiveness (MASI scores) from a total of 2 studies. The results of each study regarding the effectiveness of neoretin discrom product containing N-acetyl glucosamine (NAG) in reducing MASI scores are summarized in Table 2 above. The meta-analysis revealed that use of neoretin discrom product, significantly reduced hyperpigmentation, as stated in decreased MASI scores, with a pooled standardized mean difference (SMD) of -2.41 (95% CI: -3.86 to -0.97; p=0.001; I^2 = 76%).

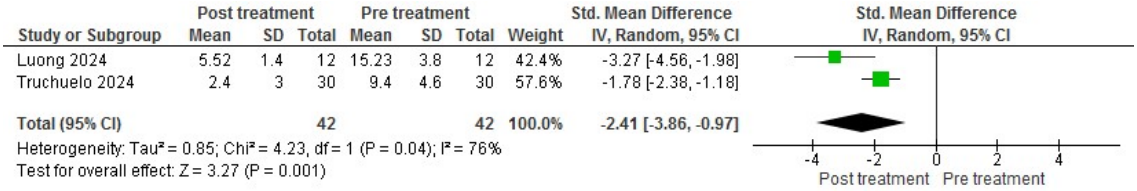

Figure 6. Analysis of MASI score changes as a parameter of hyperpigmentation after treatment with neoretin discrom product containing NAG in melasma patients

DISCUSSION

Currently, melasma is a common pigmentation disorder, particularly among Asian populations, and its treatment remains a challenge for dermatologists due to unsatisfactory responses and a high recurrence rate in many patients [10]. N-Acetylglucosamine (GlcNAc), also known as 2-acetamino-2-deoxy-β-D-glucose or 2-(acetylamino)-2-deoxy-D-glucose, is a monosaccharide derivative of glucose that is widely distributed in nature. The molecular formula of this amino monosaccharide is $C_8H_{15}NO_6$, with a molecular weight of 221.21 g/mol. In general, GlcNAc appears as a white crystalline powder with a slightly sweet taste and a melting point of 221°C. It is 25% soluble in water, and a 1% aqueous solution is clear and colorless [11]. In recent years, there has been a paradigm shift in the management of chemical peeling, with a growing preference for combining it with other procedures such as microneedling to enhance clinical outcomes. The addition of depigmenting agents such as N-acetylglucosamine has been reported to produce better improvement and more favorable results in patients with melasma [12].

This meta-analysis revealed that use of NAG in combination, not significantly reduced hyperpigmentation, as stated in not significantly decreased MASI scores, with a pooled standardized mean difference (SMD) of -1.14 (95% CI: -2.82 to 0.54; p=0.18; I^2 = 95%), whereas the use of neoretin discrom product, significantly reduced hyperpigmentation, as stated in decreased MASI scores, with a pooled standardized mean difference (SMD) of -2.41 (95% CI: -3.86 to -0.97; p=0.001; I^2 = 76%). These results indicate that the use of neoretin discrom control products containing NAG as a therapy for melasma is effective in reducing hyperpigmentation, as reflected by the improvement in MASI scores.

Several clinical studies have evaluated the effectiveness of N-acetyl glucosamine (NAG) in the management of melasma, either as monotherapy or in combination with other agents. Iraji et al. (2009) demonstrated that the combination of NAG and niacinamide had slightly greater effectiveness compared to hydroquinone, with fewer adverse effects, although the difference was not statistically significant. Nonetheless, NAG was reported to be effective in treating melasma [13]. Similarly, Manfreda et al. (2023) compared politranexamide with a combination of NAG, ethyl linoleate, and phenyl ethyl resorcinol, and found that both groups experienced a reduction in MASI scores by week 12, with no significant difference between them—indicating comparable efficacy in reducing hyperpigmentation [14]. Other studies have provided more consistent evidence of NAG's benefits. Bissett et al. (2007) reported that topical 2% NAG effectively reduced facial hyperpigmentation, and when combined with 4% niacinamide, the depigmenting effect was even greater, with excellent skin tolerability [15]. Kimball et al. (2010) reinforced these findings, showing that the niacinamide + NAG combination was significantly more effective than the control in reducing facial spot area and hypermelanization—outperforming even SPF 15 sunscreen [16].

Recent studies have also evaluated Neoretin Discrom Control–based formulations containing N-acetyl glucosamine (NAG). Luong et al. (2022) reported a 64% reduction in MASI after four months of therapy, accompanied by a 30.4% decrease in melanin index [17]. Millan et al. (2016) found an average 50% decrease in MASI scores ($p < 0.0001$), with more than 65% of patients showing clinical improvement and 77% reporting enhanced skin brightness [18]. Catala et al. (2023) similarly observed a 48% reduction in MASI at the end of treatment, with visible improvement as early as day 30 [19]. Meanwhile, Truchuelo et al. (2014) reported that Neoretin Discrom Control gel cream containing NAG produced a 70% clinical improvement after three months, comparable to hydroquinone, but with a better safety profile [20].

Theoretically, the mechanism of NAG in managing melasma is related to its ability to inhibit tyrosinase glycosylation, a key enzyme in melanogenesis. N-acetyl glucosamine (NAG) reduces melanin production in melanocytes, thereby improving hyperpigmentation and skin tone. It inhibits the conversion of pro-tyrosinase to tyrosinase and also affects genes involved in pigmentation. Tyrosinase acts as the rate-limiting enzyme in melanin synthesis; disruption of its glycosylation leads to impaired enzyme maturation and decreased enzymatic activity, resulting in lower melanin production within melanocytes [21,22].

Melanin is the primary pigment responsible for the coloration of human skin, hair, and eyes, produced by melanocytes through the process of melanogenesis. Melanogenesis and skin pigmentation serve as the most important photoprotective mechanisms, shielding the skin from damage caused by ultraviolet (UV) radiation and reducing the risk of skin carcinogenesis due to sun exposure. Abnormal loss of melanin leading to depigmentation can cause both aesthetic and

dermatological problems, while excessive melanin synthesis and pigment accumulation occur in various skin disorders, one of which is melasma. Although melanogenesis is a complex process involving numerous enzymatic and chemical reactions, enzymes such as tyrosinase and other tyrosinase-related proteins (TYRP1 and TYRP2) play crucial roles in melanin synthesis. Tyrosinase is a copper-containing metalloenzyme with two copper ions (dinuclear copper ions) that functions as the rate-limiting enzyme in melanin synthesis. Moreover, tyrosinase is considered a key factor in diseases associated with excessive melanin production. Therefore, controlling the activity of this enzyme through tyrosinase inhibitors is an important strategy for treating hyperpigmentation disorders. To date, many effective tyrosinase inhibitors have been identified and developed for use in medical and cosmetic applications, one of which is N-acetyl glucosamine. In the medical field, tyrosinase inhibitors are also recognized as an important class of clinical anti-melanoma agents, although only a few compounds are known to be both effective and safe, including N-acetyl glucosamine [23,24].

This study has several limitations. First, the number of studies included in this systematic review is relatively small, which may affect the validity of the findings and conclusions. The included studies also had relatively small sample sizes. Another limitation is the limited number of studies that specifically examined N-acetyl glucosamine (NAG) alone, without combination with other agents, in improving hyperpigmentation among melasma patients. Despite these limitations, this study offers several strengths. We believe that our findings provide valuable insights into the effectiveness of NAG therapy, offering dermatologists an alternative option for melasma management. Moreover, this review serves as a useful source of information for patients seeking to understand available treatment options for melasma, particularly those involving N-acetyl glucosamine.

CONCLUSION

N-acetyl glucosamine (NAG) alone, in combination or neoretin discrom control products containing NAG may be effective in reducing hyperpigmentation in melasma. It improves both MASI scores and the appearance of hyperpigmentation, whether used as monotherapy, in combination or as neoretin discrom products. However, from meta-analysis, combination therapy with N-acetylglucosamine (NAG) did not significantly reduce hyperpigmentation, while neoretin Discrom products showed a significant reduction in MASI scores. Moreover, NAG demonstrates excellent skin tolerability and can enhance skin brightness significantly. Based on these findings, N-acetyl glucosamine can be considered a safe and effective alternative for the management of melasma, suitable for use as a standalone therapy or as part of combination depigmentation regimens.

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Competing interests

The authors have no competing interests to declare.

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