



## **Nicotinamide as a Skin Whitener: Evidence and Controversies**

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### **Author's contribution**

*The sole author designed, analysed, interpreted and prepared the manuscript.*

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### **ABSTRACT**

**Background:** Topical nicotinamide (NAM) can reduce excessive melanin deposition in cell culture, by reversibly blocking the transfer of melanosomes from melanocytes to the adjacent keratinocytes. Thus, it has been increasingly used as a whitening agent.

**Objective:** To assess the efficacy and safety of topical nicotinamide used for the treatment of melasma and hyperpigmentation.

**Methods:** An electronic search for topical nicotinamide was carried out on Pubmed and Medline databases to identify studies that addressed this topic as a whitening agent. And to review the primary and secondary outcomes.

**Results:** A significant decrease in hyperpigmentation and increased skin lightness was found with the use of topical nicotinamide, compared with the vehicle In two small sample size clinical studies. Combined regimens including nicotinamide and other ingredients offer more synergistic effects than monotherapy.

**Conclusion:** Due to the lack of sufficient evidence, the use of nicotinamide for melasma remains controversial. Extended randomized, double-blind, placebo-controlled trials with long-term follow-up periods are needed to assess the efficacy of nicotinamide as a whitening agent.

**Keywords:** *Topical nicotinamide; whitening agent; hyperpigmentation.*

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## ABBREVIATIONS

*NAM* : Nicotinamide  
*NAD* : Nicotinamide adenine dinucleotides  
*NADP* : Nicotinamide adenine dinucleotides phosphate  
*PAR-2* : Keratinocyte protease-activated receptor  
*AHA* : Alpha hydroxyl acid  
*BHA* : Beta hydroxy acid  
*MASI* : Melasma area and severity index

## 1. INTRODUCTION

Niacin, also known as nicotinic acid or vitamin B3, is a water-soluble vitamin. It is the generic descriptor of two forms: niacin (nicotinic acid) and niacinamide (nicotinamide), based on a pyridine ring bound to a carboxylic group or a carboxamide group, respectively [ Fig. 1].

Niacin is obtained in the diet in the form of nicotinic acid, nicotinamide, and tryptophan, with the last of these transformed into nicotinamide adenine dinucleotides NAD and nicotinamide adenine dinucleotides phosphate NADP. These two compounds play a central role in energy metabolism and the cellular oxidation-reduction reactions of metabolic processes as hydride ion receptors [1].

Topically, NAM has an epidermal barrier function, antiaging properties, anti-inflammatory, and sebostatic activities, making it beneficial for treating several dermatological disorders such as psoriasis, actinic keratosis, acne, and rosacea. The NAD precursor of nicotinamide prevents the depletion of cellular energy and therefore has

photoprotective and anticarcinogenic properties [2-4].

In part, skin pigmentation results from the transfer of melanosomes synthesized by melanocytes to the surrounding keratinocytes. Suggested mechanisms for melanosomal transfer include fusion of plasma membranes, exocytosis, transfer by membrane vesicles, and cytophagocytosis [Fig. 2] [5]. The keratinocyte protease-activated receptor (PAR-2) supports the phagocytosis theory. It controls melanosome ingestion and phagocytosis by keratinocytes. Any changes in PAR-2 activity can enhance or inhibit melanosome transfer and affect pigmentation [6]. Nicotinamide can block the transfer of melanosomes to keratinocytes by inhibiting the cell-signaling pathway PAR-2 and other keratinocyte factors to decrease melanogenesis [7,8].

Various formulations that include creams, gels, serums, and powder with concentrations ranging from 2 to 10%, have been used in treatment for a period of four to eight weeks. Whether cream or serum is used, it is important to start with a low concentration (2%), particularly on those with sensitive skin. There are a variety of preparations in the market, some containing nicotinamide alone and others including additional ingredients, such as hyaluronic acid, AHA, BHA, and ascorbic acid. A high-strength serum contains 10% nicotinamide with 1% zinc available. This high amount of nicotinamide helps to reduce pigmentation and is balanced by a small amount of zinc to maintain sebum activity.

The present study reviews the evidence-based efficacy and safety of nicotinamide in the treatment of melasma and hyperpigmentation.

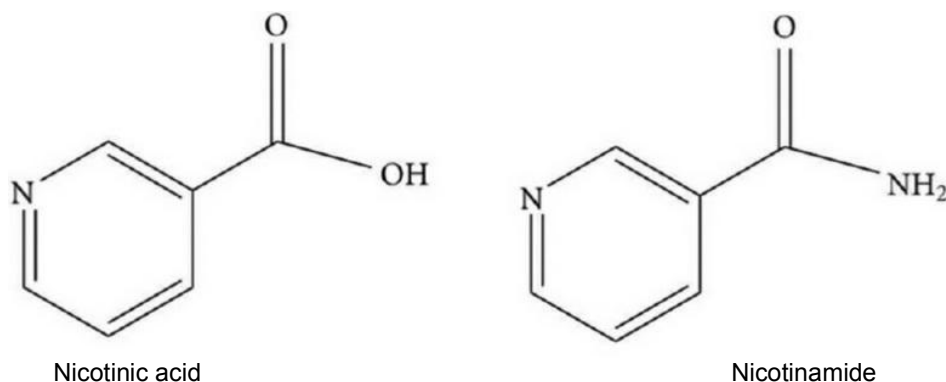
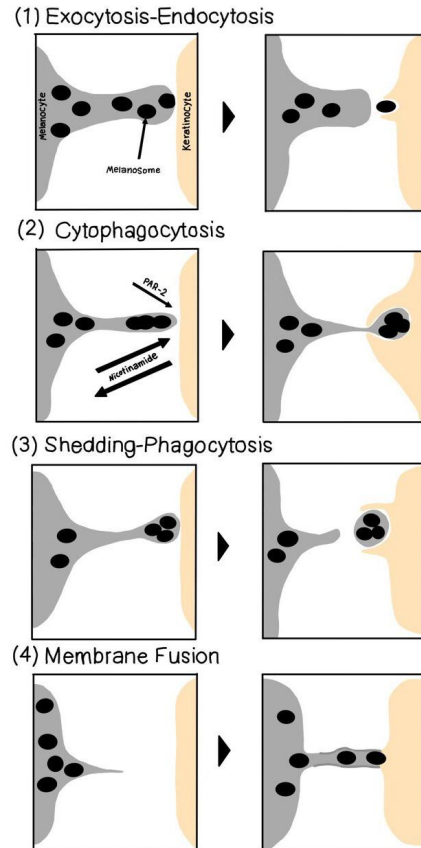


Fig. 1. Chemical structures of nicotinic acid and nicotinamide



**Fig. 2. Suggested mechanisms for melanosomal transfer from melanocytes to the keratinocytes**

## 2. METHODS

An electronic search for the following (nicotinamide, melasma, and hyperpigmentation) was carried out on Pubmed and Medline databases to identify studies that included this topic. A total of six studies were selected for this review to determine the efficacy of nicotinamide as a whitening agent. Case reports were excluded from this study. The review dealt with the design of each study, the number of patients, and the efficacy profiles of the treatment regimen followed. Data were collected and analyzed to identify the efficacy and safety profiles of topical NAM in hyperpigmented disorders.

## 3. RESULTS

The efficacy of topical nicotinamide as monotherapy for melasma has been evaluated in many studies. Although most of these studies had a small sample size, ranging from 17-27 patients, they have reported a significant effect

through the alteration of MASI scores from the baseline.

A clinical study that investigated 5% nicotinamide in 18 subjects with hyperpigmentation found a significant decrease in their hyperpigmentation and increased skin lightness, compared with the vehicle alone, after four weeks of use [8]. In a double-blind, randomized clinical trial, 27 patients using 4% topical nicotinamide on half of their face and 4% hydroquinone on the other half for eight weeks showed that both treatments improved melasma, by 44% and 55% respectively [9]. Milder side effects were reported on the nicotinamide side compared to the hydroquinone side, 18% and 29% respectively.

A combined formulation containing nicotinamide plus tranexamic acid was tried on 42 Korean patients with melasma. It resulted in reducing irregular pigmentation, providing an effect beyond that achieved by sunscreen [10]. In a 10-week, double-blind, vehicle-controlled, parallel-group study, conducted on (n= 101) patients, it

**Table 1. Comparing the six studies with regard to the design, the number of patients, type of treatment, and efficacy profile**

Study	Design	Subjects	Type of treatment	Efficacy
Hakozaki T, et al.	Paired design	18	Monotherapy	Significant $P < 0.05$
Navarrete-Solís J, et al.	Double-blind, left-right, randomized clinical trial	27	Monotherapy	Significant $P < 0.05$
Lee DH, et al.	Randomized, double-blind, vehicle-controlled trial.	42	Combined nicotinamide plus tranexamic acid	Significant $P < 0.05$
Kimball AB, et al.	Randomized, double-blind, vehicle-controlled trial.	101	Combined nicotinamide plus N- acetyl glucosamine( NAG)	Significant $P < 0.05$
Crocco EI, et al.	A prospective, open-label study	33	Combined nicotinamide 4%, arbutin 3%, bisabolol 1%, and RAL 0.05%	Significant $P < 0.05$
Viyoch J, et al. <sup>20</sup>	Randomized, double-blind, controlled study	33	combination of trans-4-(aminomethyl) cyclohexanecarboxylic acid/potassium azeloyl diglycinate/niacinamide compared with an emulsion-based control	Significant $P = 0.005$

was found that combined topical nicotinamide with N-acetyl glucosamine was significantly more effective than a vehicle-controlled formulation in reducing the appearance of facial spots and hyperpigmentation [11]. Crocco EI et al. [12] reported the significant efficacy and safety of a novel cream formulation containing nicotinamide 4%, arbutin 3%, bisabolol 1%, and retinaldehyde 0.05% in 33 participants with epidermal melasma (Table 1).

The most common side effects were pruritus, erythema, and burning, and all were reduced with continued treatment [6].

The results in these studies need to be elucidated due to the limitations in the study design. These limitations include a small sample size, short study period, and lack of long-term follow-up.

#### 4. DISCUSSION

With the assistance of Wood's light examination, melasma may be classified into four types, according to the depth of melanin deposition. The most common type is epidermal melasma, followed by dermal, mixed, and indeterminate types, depending on the level at which the pigmentation appears intense under Wood's

lamp [13]. Melasma results from the increased deposition of melanin in the epidermis (keratinocytes), in the dermis within (melanophages), or both. Ultrastructural studies have reported an increase in the size of melanosomes within the melanocytes and keratinocytes of melasma patients [14]. Nicotinamide can reduce excessive melanin deposition by reversibly blocking the transfer of melanosomes from melanocytes to the adjacent keratinocytes, and is thus more effective against epidermal melasma [15].

Most topical treatments for melasma have focused on the inhibition of enzymatic activation that creates excessive melanin formation. However, the results may be conflicting, as melasma can recur due to the melanosomal transfer or migration of new melanocytes from hair follicles to the skin surface, leading to the recurrence of hyperpigmentation. Using nicotinamide at this stage can reduce the likelihood of recurrence by inhibiting this mechanism. The standard treatment for melasma includes hydroquinone and other bleaching agents, but the long-term use of these products may cause concern due to their instability and adverse effects, such as ochronosis and dyspigmentation [16]. Conversely, nicotinamide is more stable and not affected by emollients,

acids, alkaline, and oxidizing substances. Besides, the adverse effects of topical nicotinamide are rare and related to drug concentration. These include transient erythema, itching, and burning sensations.

Nicotinamide has a photoprotective effect. It prevents ultraviolet radiation from reducing ATP levels and inhibiting glycolysis, which induces an energy crisis. It, therefore, enhances DNA repair after damage by sunlight and reduces the UV-induced suppression of immunity [17,18]. For these reasons, nicotinamide was considered as a potential agent in topical sunscreens. Topical skin whitening serum containing NAM in its formulation, had favorable outcomes in treating melasma in twelve healthy Caucasian women [19].

Nicotinamide is also available in the form of mesotherapy solutions, applied by derma roller to create microchannels that allow better absorption of the drug, increasing its effectiveness. Cosmeceutical companies have manufactured solutions containing nicotinamide and antioxidants including glutathione and ascorbic acid for use by intradermal injection; however, no clinical studies support this modality. Despite the safety and efficacy, no definitive evidence currently exists for recommending the intradermal and micro needling use of nicotinamide for melasma.

Regardless of the advantages of nicotinamide, its use to treat melasma remains controversial, due to the scarcity of evidence-based studies. Only four randomized, double-blind studies were found using a limited number of patients; one used nicotinamide alone and the other used it combined with other ingredients. No evidence has been found to recommend the intradermal use of nicotinamide for melasma.

## 5. CONCLUSION

Although the mechanism of action of nicotinamide supports the whitening effect, there is conflicting evidence regarding its use in treating melasma. Small sample size studies were conducted to use topical NAM with short follow-up periods. Due to the lack of sufficient evidence, the use of nicotinamide for melasma remains controversial. Extended randomized, double-blind, placebo-controlled trials with long-term follow-up periods are needed to assess the efficacy of nicotinamide as a whitening agent.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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