

## **Niacinamide for the treatment of melasma: an integrative review of randomized clinical trials**

**Niacinamida para o tratamento do Melasma: uma Revisão Integrativa de Ensaio Clínicos Randomizados**

**Niacinamida para el tratamiento del melasma: una revisión integradora de ensayos clínicos aleatorios**

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### **Abstract**

**Introduction:** Melasma is a very common and difficult to treat hypermelanosis because it usually responds poorly to therapies, negatively affecting the quality of life of patients. **Objective:** to know and analyze the scientific evidence related to the treatment of patients with facial melasma treated with niacinamide. **Method:** a literature review was performed based on a data search in BIREME, PubMed, SciELO and ScienceDirect. Articles indexed in these electronic journals were included in the time frame from 2011 to 2019. **Results:** Evidence analyzes revealed a major impact on the appearance of facial melasma after niacinamide treatment. Well, the studies (100%) concluded improvement of the spots with the treatment time, improving the appearance of the skin. **Conclusion:** Evidence shows that niacinamide has a lightening property in adult women with improvement of melanic hyperpigmentation caused by melasma. However, there is very little evidence published in the last decade using pure niacinamide for increased pigmentation in melasma.

**Keywords:** Melasma; Niacinamide; Skin pigmentation; Quality of life.

### **Resumo**

**Introdução:** O melasma é uma hipermelanose bastante comum e de difícil tratamento porque geralmente responde mal as terapias, afetando negativamente a qualidade de vida dos pacientes. **Objetivo:** conhecer e analisar as evidências científicas relacionadas ao tratamento de pacientes com melasma facial tratados com niacinamida. **Método:** foi realizada uma revisão de literatura com base em uma busca de dados no BIREME, PubMed, SciELO e ScienceDirect. Os artigos indexados nesses periódicos eletrônicos foram incluídos no espaço temporal de 2011 até 2019. **Resultados:** As análises das evidências revelaram impacto importante na aparência do melasma facial após o tratamento com niacinamida. Pois, os estudos (100%) concluíram melhora das manchas com o tempo de tratamento, melhorando a aparência da pele. **Conclusões:** As evidências mostram que a niacinamida possui propriedade clareadora em mulheres adultas com melhora da hiperpigmentação melânica causada pelo melasma. No entanto, há pouquíssimas evidências publicadas na última década com uso da niacinamida pura para pigmentação aumentada no melasma.

**Palavras-chave:** Melasma; Niacinamida; Pigmentação da pele; Qualidade de vida.

### **Resumen**

**Introducción:** El melasma es una hipermelanosis muy frecuente y de difícil tratamiento, ya que suele responder mal a las terapias, afectando negativamente la calidad de vida de los pacientes. **Objetivo:** conocer y analizar la evidencia científica relacionada con el tratamiento de pacientes con melasma facial tratados con niacinamida. **Método:** se realizó una revisión de la literatura a partir de una búsqueda de datos en BIREME, PubMed, SciELO y ScienceDirect. Los artículos indexados en estas revistas electrónicas se incluyeron en el período de 2011 a 2019. **Resultados:** los análisis de evidencia revelaron un impacto importante en la aparición del melasma facial después del tratamiento con niacinamida. Pues bien, los estudios (100%) concluyeron mejora de las manchas con el tiempo de tratamiento,

mejorando el aspecto de la piel. Conclusiones: La evidencia muestra que la niacinamida tiene una propiedad aclarante en mujeres adultas con mejoría de la hiperpigmentación melánica causada por el melasma. Sin embargo, hay muy poca evidencia publicada en la última década sobre el uso de niacinamida pura para el aumento de la pigmentación en el melasma.

**Palabras clave:** Melasma; Niacinamida; Pigmentación de la piel; Calidad de vida.

## 1. Introduction

Melasma is a very common and difficult to treat hypermelanosis because it usually responds poorly to therapies, negatively affecting patients' quality of life. Melasma is a complex interaction between epidermal melanocytes, keratinocytes, dermal fibroblasts, mast cells, and vascular endothelial cells. Factors that influence the onset of melasma include inflammation, reactive oxygen species, ultraviolet radiation, genetic and hormonal factors (Sarkar et al., 2020).

Considered an acquired skin disease, melasma is characterized by symmetrical patches of hyperpigmentation in areas exposed to the sun, such as the cheekbones and cheeks, forehead (forehead), chin (chin), nose and upper lips. Histological features differentiate it into epidermal, dermal pigmentation, solar elastosis, increased vascularization, and mastocytosis (Know et al., 2016).

From the perspective of the pathogenesis of melasma, it is known that exposure to ultraviolet (UV) radiation causes hyperactivity of melanocytes in the skin, leading to an increased production of organelles called melanosomes. The synthesis of melanin follows an enzymatic order, which is synthesized from the enzymatic conversion of tyrosine into the pigment melanin, responsible for determining the skin phototype and photoprotection against UV radiation (Vashi & Kundu, 2013; Passeron & Picardo, 2018; Yuan & Jin, 2018).

The melanin pigment is distributed in melanocytes and is then transferred to adjacent keratinotics. In addition to keratinotics, fibroblasts and immune cells also interact with melanocytes through paracrine secretions in response to sunlight exposure and inflammation (Yuan & Jin, 2018). Fibroblasts also participate as signaling modulating agents for melasma, stimulating melanogenesis and melanosome transfer (Kang et al., 2011; Kim et al., 2013). In addition, photoaged skin fibroblasts produce more promelanogenic growth factors such as, for example, keratinotic growth factor (KGF), hepatocyte growth factor and stem cell factor (SCF) (Briganti et al., 2013).

As noted, melasma develops in specific areas such as cheeks, forehead and lips. The reason for this “specificity” can also be explained by the presence of sebaceous glands, since they can secrete interleukin-1 $\alpha$  (IL- $\alpha$ ), IL-6, angiopoietin and adipokine, and these factors can induce melanogenesis. (Abdel-Naser et al., 2012). Much of this statement suggests that the intensification of the rhythm of melanogenesis also calls into question the oxidation of skin surface lipids by UV radiation, which can activate the synthesis of melanin in melanocytes, providing greater oxidative stress in favor of melasma (Picardo et al., 1991; Kuthial et al., 2019).

Skin with melasma has an increased amount of melanin in the epidermis and dermis compared to skin without melasma. (Kang et al., 2002). Aspect that is linked to the increase in melanin-containing cells in the granular, spinous and basal cell layers (Zeng et al., 2020). In addition to these aspects, it is suggested that the rupture of the basement membrane may facilitate the migration of melanocytes and melanin to the dermis, being observed as free melanocytes or melanophages frequently identified in skin samples with melasma (Lee et al., 2012).

The etiology of melasma is still poorly understood, with an incidence ranging from 1% to 50% in the world population (Ogbechie-Godec & Elbuluk, 2017). Melasma is known to be more prevalent in women of Asian, Latin American, Middle Eastern and African descent, given multifactorial causes such as increased skin pigmentation, changes in hormone levels, family history, and sun exposure (Passeron, 2013; Lee, 2015). Melasma has a great impact on psychosocial aspects, generating negative repercussions on self-esteem, depression and social isolation (Jiang et al., 2017).

The treatment of melasma still remains a major challenge for professionals working in facial aesthetics. For this hyperpigmentation, topical agents are the mainstay of therapy. However, first-line therapeutic options most often focus on Hydroquinone (HQ) and triple combinations of topical treatment (HQ, retinoid, steroid). For the second choice, the use of chemical peels and laser therapies stand out (Sheth & Pandya, 2011). However, the continuous and unprofessional use of the HQ has aroused a massive concern about the appearance of Ochronosis, which is a bluish-gray discoloration of the skin as a result of prolonged use of the HQ (Sheth & Pandya, 2011).

Other therapeutic approaches to melasma are based on the use of antioxidants, considering that oxidative stress has a defined role in the pathophysiology of melasma. Discussions on this topic include the use of vitamin C, azelaic acid, cysteamine, glutathione, carotenoids and the application of various other antioxidants in this and other hyperpigmentation disorders. Where evidence points to promising results with topical as well oral preparations (Babbush et al., 2020).

Over time, treatment therapies for melasma have gained more and more space, emerging numerous investigations using topical compositions, such as niacinamide, an amide of vitamin B3 (niacin), where past in vitro studies have demonstrated relevant dermatological properties, such as such as: antimicrobial effect, synthesis of ceramids, inhibition of melanosome transfer, anti-inflammatory effect, sebostatic effect, increased capillary permeability, as well as inhibition of nitric oxide (Wohlrab & Kreft, 2013).

It is worth mentioning that the treatment of melasma, while chronic hyperpigmentation results only in palliative treatments, since there is no total remission of melasma in currently available therapies. This is because after treatment, if the patient is exposed to factors that influence melasma, it can reappear (Pollo et al., 2018). That said, it is reaffirmed that the management of melasma is very challenging because, as suggested in the literature, it is not (Kwon et al., 2019), only a dysfunction of melanocytes, but also a condition of skin photoaging. In such a way that the histopathological findings show solar elastosis, alteration of the basement membrane, increased vascularization and mast cell count (Kwon et al., 2019).

Brazil is a country with a high rate of miscegenation with a predominantly tropical climate, which favors the development of melasma in 15-35% of adult Brazilian women (BSD, 2006). Despite being asymptomatic, the face is the main area of melasma involvement in women of childbearing age, which has a negative impact on body image, interpersonal relationships and perception of quality of life (Pollo et al., 2018).

Therefore, this study was developed in view of the need for facial aesthetic professionals to investigate and evaluate the therapeutic quality of niacinamide in patients with melasma, thus contributing to the development of clinical reasoning aimed at improving skin quality. In this sense, the objective of this review was to know and analyze the scientific evidence related to the treatment of patients with facial melasma treated with niacinamide.

## **2. Methodology**

This review is qualitative exploratory descriptive research of the Integrative Literature Review type, carried out based on a problem/hypothesis question, evaluation and analysis of the data found in the published evidence and description of the results obtained (Snyder, 2019).

To search for articles in the literature, the following databases were used: Online Scientific Electronic Library (SciELO), Latin American and Caribbean Center for Health Sciences Information (BIREME), PubMed and ScienceDirect. The descriptors, and their combinations in English, used to search the articles were: niacinamide, melasma, niacinamide skin, niacinamide anti-melanogenesis, through search strategies using the AND Boolean operator.

The inclusion criteria defined for the selection of articles used in this study were: articles published in English, complete articles and published in the databases in the last ten years (2012-2022). The exclusion criteria applied were inadequate methodology and study design, combined niacinamide formulations, unpublished studies, opinions and incomplete

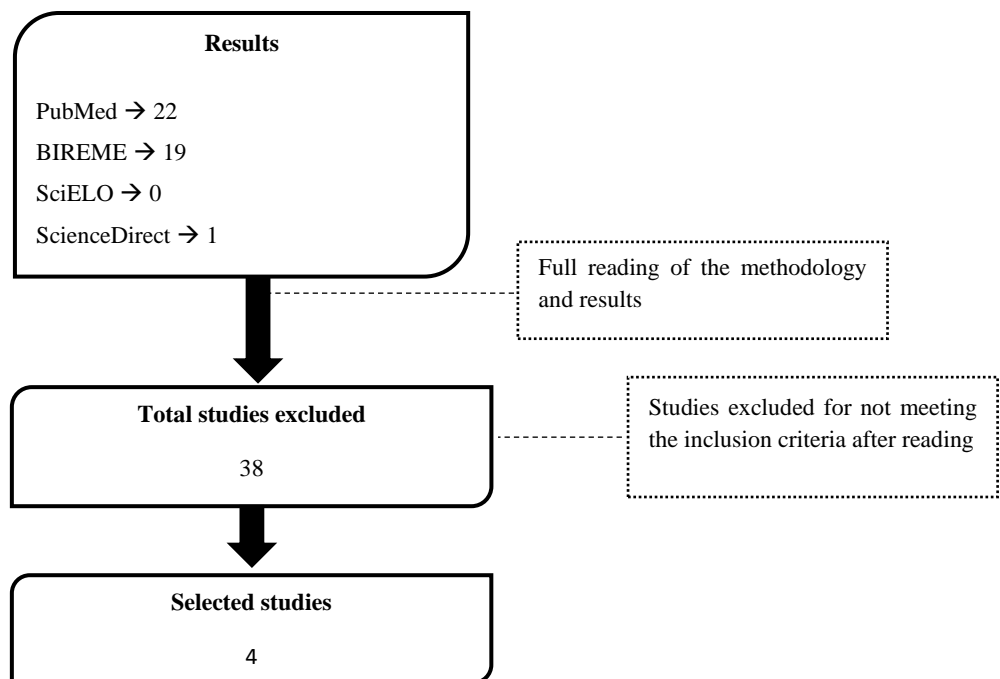
studies.

The information obtained was synthesized and organized for the construction of the development of this study, as follows: author, title, journal, year of publication, treatment protocol used, active concentration (%), sample number, type of melasma, results and conclusion. The results were critically analyzed and presented according to the method chosen to achieve proposed objective.

### 3. Results

The bibliographic search identified 42 articles in the digital repositories used in the research. A total of 38 articles were excluded after reading the methodology, as these did not meet the central objective of this study. That is, they did not address the treatment of melasma with the active ingredient niacinamide alone. Thus, the number of selected studies consisted of four articles, as can be seen Figure 1.

**Figure 1.** Flowchart of the methodological step for article selection.



Source: Authors (2022).

All articles are configured as intervention studies, in which the design sought to treat patients with melasma through the topical use of niacinamide, reasons that meet the proposed objectives. The selected articles were published between 2011 and 2019, as shown in Table 1.

The studies were developed in different countries, such as Brazil, 25% (Santos-Caetano et al., 2019), Mexico, 50% (Navarrete-Solís et al., 2011; Campuzano-García et al., 2019) e Korea, 25% (Lee et al., 2016) Table 1, demonstrating that interest in niacinamide for the treatment of melasma transcends geopolitical divides.

**Table 1.** List of articles included in this literature review

N°	Title	Author/Year	Journal	Methods	Conclusion
1	A Double-Blind, Randomized Clinical Trial of Niacinamide 4% versus Hydroquinone 4% in the Treatment of Melasma	Navarrete-Solís et al., 2011	Dermatology Research and Practice	<b>Group:</b> 4% niacinamide; Group: 4% hydroquinone - for 8 weeks	Effective, integral and safe alternative therapeutic niacinamide for melasma, reducing pigmentation and inflammation
2	<i>In vivo</i> anti-melanogenesis activity and in vitro skin permeability of niacinamide-loaded flexible liposomes (Bounsphere™)	Lee et al., 2016	Journal of Drug Delivery Science and Technology	Niacinamide 3x a week – for 8 weeks	Niacinamide 2% improved melasma, working as a skin whitening agent
3	DNA Methyltransferases in Malar Melasma and Their Modification by Sunscreen in Combination with 4% Niacinamide, 0.05% Retinoic Acid, or Placebo	Campuzano-García et al., 2019	BioMed Research International	<b>Group:</b> 4% niacinamide; Group: 0.05% retinoic acid; <b>Group:</b> placebo – nightly applications for 8 weeks	Significant reduction of specific staining in melasma lesions in the niacinamide group
4	Cosmetic benefits of a novel biomimetic lamellar formulation containing niacinamide in healthy females with oily, blemish-prone skin in a randomised proof-of-concept study	Santos-Caetano et al., 2019	International Journal of Cosmetic Science	<b>Test group:</b> 4% niacinamide + facial cleanser; <b>Control group:</b> facial cleanser only; <b>Positive control group:</b> commercial 4% niacinamide (Acneicinamide®) + cleanser containing 2% salicylic acid – for 8 weeks	Significant difference was achieved in favor of the test group in the total spot count at 8 weeks. Niacinamide provided an overall improvement in the skin appearance of people with blemish-prone skin

Source: Authors.

Of the selected journals, one (Table 1, nº1) was in the dermatological area related to the prevention, diagnosis and treatment of skin, hair and nail disorders. Two of them (Table 1, No. 2 and 4) were dedicated to drug delivery and pharmaceutical technology, as well as cosmetic research. Finally, the last one (table 1, nº 3), focused on a wide range of subjects within the biomedical sciences through basic and translational research.

The instrument for analyzing the methodological quality of the studies selected to assess the response to treatment with niacinamide in patients with melasma found that all (100%) used the treatment concomitantly during eight weeks of treatment (Table 1). However, three articles (75%) did not refer to the complete dosage (nº 1, 2, 4), that is, whether niacinamide was applied during the day or night, or in both situations.

The level and follow-up of melasma in respondents were determined by clinical examination using the Melasma Area and Severity Index (MASI) and other important instruments for analyzing melasma in relation to skin appearance (Table 2). Evidence analyzes revealed a major impact on the appearance of facial melasma after niacinamide treatment. Well, the four studies (100%) concluded improvement of the spots with the treatment time, improving the appearance of the skin.

This study showed consistency and good correlation in the improvement of melasma with the use of topical 4% niacinamide, demonstrating that this topical agent can be used for this condition of pigmentation of the face and improves the quality of life of Brazilian, Mexican and Korean female patients.

**Table 2.** Melasma assessment instruments used in the studies.

Nº	Title	Author/Year	Melasma (pigment) assessment
1	A Double-Blind, Randomized Clinical Trial of Niacinamide 4% versus Hydroquinone 4% in the Treatment of Melasma	Navarrete-Solís et al., 2011	Chromameter (CR-300; Minolta, Osaka, Japão), Melasma Area and Severity Index (MASI), Investigator's Global Assessment (IGA) by an independent observer, conventional photography and infrared thermography (Flexcam S, Infrared solutions, USA) with photographic record that was used primarily to detect irritation
2	<i>In vivo</i> anti-melanogenesis activity and <i>in vitro</i> skin permeability of niacinamide-loaded flexible liposomes (Bounsphere™)	Lee et al., 2016	Janus Facial Analysis System (PSI Well-Being, Coréia), and the melasma area (6 cm 6 cm) was measured using an Antera 3D imaging device (Miravex, Dublin, Irlanda). Then, the area of hyperpigmentation was marked on the photo and the parameters of the mexameter were recorded.
3	DNA Methyltransferases in Malar Melasma and Their Modification by Sunscreen in Combination with 4% Niacinamide, 0.05% Retinoic Acid, or Placebo	Campuzano-García et al., 2019	Melasma Activity and Severity Index (MASI) greater than seven, brightness scale (L*), for scores of 0 (total black) a 100 (total white), and the erythema axis (a*), for scores from 0 to 50.
4	Cosmetic benefits of a novel biomimetic lamellar formulation containing niacinamide in healthy females with oily, blemish-prone skin in a randomised proof-of-concept study	Santos-Caetano et al., 2019	Chromameter (CM 865 [Courage + Khazaka, Colony, Germany]); blinded rater assessments of spot counts (papules and pustules); blinded lay evaluator (ie by untrained individuals). Photo reviews (taken using a Canfield Visia imaging system [Canfield, Parsippany, EUA)

Source: Authors.

#### 4. Discussion

As mentioned, melasma is a condition of hyperpigmentation of the skin and is mostly asymptomatic in exposed areas, such as the face. It mainly affects women of childbearing age, causing dissatisfaction with their own image, directly interfering with their quality of life, how they behave and present themselves (Pollo et al., 2018).

When the quality of life in patients of both sexes with melasma in Brazil was investigated using a validated questionnaire for this purpose, it was predominantly observed that patients reported discomfort due to the stains (65%), frustration (55%) and constriction (57%) with the appearance of the skin (Cestari et al., 2006). This clearly shows that melasma affects the quality of life of Brazilian patients and that it is necessary to search for effective treatments to reduce the clinical severity of melasma.

Niacinamide used as a cosmetic formulation showed safety at a concentration of 4% (Cosmetic Ingredient Review Expert Panel, 2005). However, new research must be more robust to be able to describe proven positive effects based on evidence-based, low-bias practice.

In a prospective, comparative, randomized, intraindividual, double-blind study of the treatment of melasma (Giansante et al., 2020), the authors compared the efficacy and adverse effects of a triple combination versus topical niacinamide (group A) and a triple combination versus tranexamic acid. The results revealed after 8 weeks of treatment that most patients reached the classification of mild melasma, in addition, all treatment modalities showed similar responses, with no adverse effect for topical niacinamide. In this sense, this fact can be considered to recommend topical niacinamide for the treatment of melasma, since this formulation achieves results like those already well-known in the cosmetic market.

Cosmetology has shown that niacinamide has application in many skin disorders, such as hyperpigmentation, aging, acne, psoriasis, pruritus, dermatitis, epidermal melasma, among other clinical situations. In addition, it is argued that its continuous use contributes to healthier, brighter and hydrated skin. Therefore, these positive characteristics indicate a great potential for the use of niacinamide for future melasma therapies (Madaan et al., 2021).

As the results of this study showed that there are few randomized clinical trials in the literature using niacinamide for the treatment of melasma, it further suggests the need to evaluate the quality of niacinamide as a whitening agent in patients with melasma in cultures other than those tested in the studies of table 1. This will stimulate their reliability, consistency and decision-making power in the choice of niacinamide in relation to other depigmentants both applied to the prescription of female and male patients.

#### 5. Conclusion

Evidence shows that niacinamide has lightening property in adult women with improvement of melanic hyperpigmentation caused by melasma. However, there is little evidence published in the last decade using pure niacinamide for increased pigmentation in melasma. Therefore, new double-blind randomized controlled studies should be carried out in order to verify the effect of niacinamide in female and male patients of different nationalities and territorial regions, and your safety over a longer period.

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