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REVIEW ARTICLE

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# Nutrological control and treatment of melasma in the COVID-19 pandemic: a concise systematic review

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## Abstract

**Introduction:** In the skin disease scenario, hyperpigmentation (melasma) is present in about 14.5%-56% of pregnant women and 11.3%-46% of people taking oral contraceptives worldwide. The coronavirus disease 2019 (COVID-19) pandemic has brought great challenges to the treatment of melasma, as well as doubts about its worsening. Diet and nutrients for topical or oral use play an important role in the control of infectious diseases. **Objective:** It was to perform a concise systematic review on the occurrence, worsening, and nutrological treatment of melasma in the COVID-19 pandemic. **Methods:** The present study followed a systematic review model (PRISMA). After literary search criteria using MeSH Terms, a total of 98 clinical studies were compared and submitted to eligibility analysis and, after that, 70 studies were selected. The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile. **Results and Conclusion:** Melasma is an acquired hyperpigmentation disorder, and reactive oxygen species play an important role in the regulation of melanin synthesis. In nutrological terms, lycopene is one of the most effective oxygen neutralizers among tomato-derived carotenoids. Furthermore, hydroquinone is a compound that has been used for the treatment of hyperpigmentation by tyrosinase inhibition mechanism and can be found in wheat. Thus, an adequate knowledge of the role of nutritional supplements in dermatological diseases can be a useful tool. Based on this, there is growing interest in oral medications and dietary supplements to improve melasma. Oral medications and dietary supplements evaluated include tranexamic acid, Polypodium leucotomos extract, beta-carotenoid, melatonin, and procyanidin. Also, hydrolyzed collagen is a low molecular weight protein that has been widely used and can prevent melasma. Serum zinc levels can also predict the occurrence of melasma. Finally, there is still no report on skin darkening associated with COVID-19.

**Keywords:** Melasma. Skin hyperpigmentation. Nutrients. Dietary therapy. COVID-19.

## Introduction

In the scenario of skin diseases, hyperpigmentation (melasma) is present in about 14.5%-56% of pregnant women and in 11.3%-46% of people taking oral contraceptives worldwide **[1,2]**, mainly Hispanic and Asian women are more commonly affected by melasma **[3]**. Disease onset occurs earlier in fair-skinned types, while those with dark skin are usually associated with a late-onset **[4]**. In this sense, it can be said that melasma is a commonly acquired hyperpigmented disease that occurs mainly in photo exposed areas (face, neck, forearms, back, and neck) and mainly affects women of reproductive age **[5,6]**.

In this context, the coronavirus disease 2019 (COVID-19) pandemic brought great challenges to the treatment of melasma, as well as doubts about its worsening. Thus, it is necessary to analyze the public interest in dermatological symptoms, conditions, treatments, and procedures during the COVID-19 pandemic. One study demonstrated a significant impact of the COVID-19 pandemic on the public interest in dermatology. The present results would assist in the formulation of health policies and sources of information that meet public demand. The reasons for the observed trends and their effects on patient outcomes may be of interest for future studies **[7,8]**.

In this scenario, the diet and nutrients for topical or oral use play an important role in the control of infectious diseases. Thus, a study that was presented in the development of results of the present study intended to establish the "hypothesis of conscious, selective autophagy and self-destruction, that is, deregulated autophagy of skin and hair in a scenario of low dietary protein", determining the facial profile, presentation clinical and histopathological correlation of deficient protein intake and lack of food in a tertiary institute of skin aesthetics **[9]**.

Therefore, the present study carried out a concise systematic review on the occurrence, worsening, and nutrological treatment of melasma in the COVID-19 pandemic.

## Methods

### Study Design

The present study followed a systematic review model, following the systematic review rules – PRISMA (Transparent reporting of systematic reviews and meta-analyzes-HTTP: //www.prisma-statement.org/).

### Search Strategy and Information Sources

The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: -Search by MeSH Terms: *Melasma. Skin hyperpigmentation. Nutrients. Dietary therapy. COVID-19*, and the use of Booleans "and" between mesh terms and "or" among historical findings, following the rules of the word PICOS (Patient; Intervention; Control; Outcomes; Study Design).

### GRADE Classifications And Bias Risk

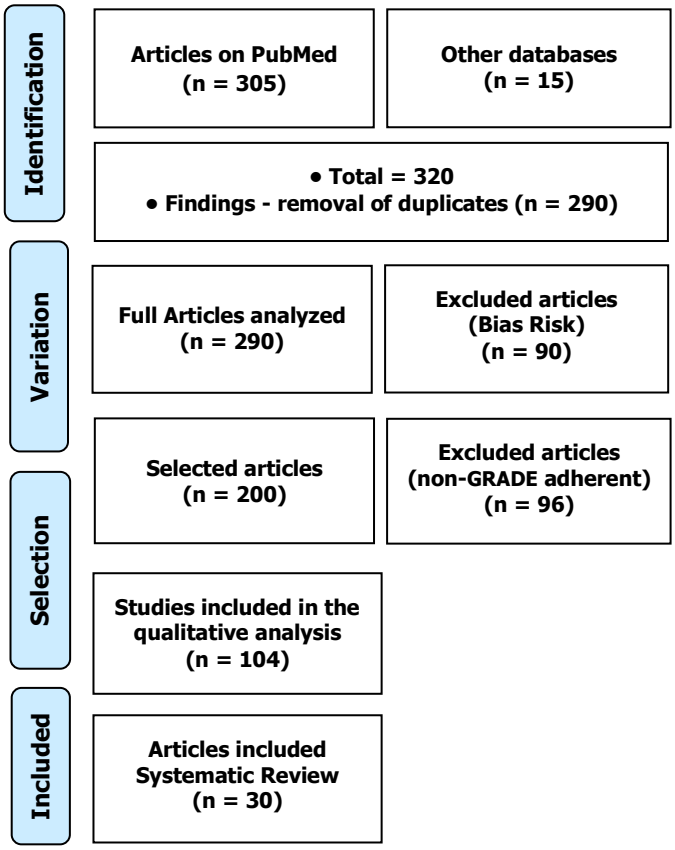
According to the Grading of Recommendatons Assessment, Development and Evaluaton (GRADE) criteria. The quality of the evidence was classified as high, moderate, low, or very low, according to the risk of bias, clarity of comparisons, precision, and consistency of the analyzes. The Cochrane instrument was to be adopted to assess the risk of bias of the included studies

## Results and discussion

### Summary Of Findings

A total of 320 articles were found involving the melasma, nutrients and COVID-19. Initially, the duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, based on the elimination of articles with biases that could compromise the reliability of the results, according to the rules of the Cochrane instrument, as well as articles that presented low quality in their methodologies, according to the GRADE classification. A total of 104 articles were fully evaluated and 30 were included in this study (**Figure 1**).

**Figure 1.** Flow Chart of Study Eligibility.




Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias (studies with a small sample size) and 70 studies with uncertain risk (studies with results without statistical significance). The domains that presented the highest risk of bias were related to the number of participants in each study addressed. In addition, there was a lack of funding sources in 2 studies and 1 studies did not disclose information about the declaration of conflict of interest.

### Major Studies – Melasma And Nutrients

After analyzing the selected studies, it was identified that melasma is an acquired hyperpigmentation disorder, and reactive oxygen species play an important role in the regulation of melanin synthesis. In this sense, in nutrological terms, lycopene is one of the most effective oxygen neutralizers

among tomato-derived carotenoids. Furthermore, hydroquinone is a compound that has been used for the treatment of hyperpigmentation by tyrosinase inhibition mechanism and can be found in wheat. Thus, a study prepared an appropriate cream formulation containing 0.05% tomato lycopene and 3.45% wheat bran extract, with physicochemical characterization. The prepared formulations were applied twice daily for three months in combination with SPF = 30 sunscreen by 22 patients diagnosed with melasma. The MASI score in two groups was assessed at weeks 0, 3, 6, 9, 12, and 1 month after treatment. The MASI score of the intervention group from the sixth week to the end of treatment was significantly decreased compared to the beginning of treatment ($p<0.05$), and the mean difference in the MASI score and the rate of skin discoloration in the treatment group intervention were significantly higher than in the placebo group. The size of melasma during the study significantly decreased from 6.59 ± 3.47 to 5.97 ± 3.83 ($p<0.05$) **[10]**.

In this sense, an adequate knowledge of the role of nutritional supplements in dermatological diseases can be a useful tool. While there are several publications on the use of nutritional supplements for the amelioration of skin conditions, most of them are based on associations or in vitro studies, but very few transcend the rigors of a blinded randomized controlled clinical trial. There appears to be some evidence in acne, psoriasis, telogen effluvium, hives, and vitiligo. Celiac disease and dermatitis herpetiformis have a strong relationship with diet. Rosacea has a strong link with certain foods, but other diseases such as melasma and aphthous stomatitis still lack sufficient evidence to support this **[11]**.

Based on this, there is growing interest in oral medications and dietary supplements to improve melasma. Thus, a systematic review study with eight randomized clinical trials evaluated the efficacy and safety/tolerability of oral medications and dietary supplements for the treatment of melasma. Oral medications and dietary supplements evaluated include tranexamic acid, Polypodium leucotomos extract, beta-carotenoid, melatonin, and procyanidin. These agents seem to have a beneficial effect in improving melasma **[12]**.

Still in this context, natural antioxidants are replacing the use of synthetic antioxidant ingredients due to their safe, nutritional, and therapeutic values. As an example, hydrolyzed collagen (HC) is a low molecular weight protein that has been widely used due to its excellent biocompatibility, easy biodegradability, and poor antigenicity. The antioxidant properties of HC are conditioned to the size of the molecule, the smaller the molecular mass of the peptides, the greater the ability to donate an electron or hydrogen to stabilize the radicals. The antioxidant capacity of HC is mainly due to the presence of hydrophobic amino acids in the peptide. The exact mechanism of the peptides that act as antioxidants is not known, but some aromatic amino acids and histidine are reported to play an important role in antioxidant activity. Oral intake of HC increases the levels of collagen-derived peptides in the bloodstream and improves skin properties such as elasticity, skin moisture, and transepidermal water loss. Furthermore, the daily intake of HC protects the skin against UV melasma, increases the production of fibroblasts and the extracellular matrix of the skin **[13]**.

Also, there are several studies on serum zinc levels in skin diseases. A prospective, cross-sectional study with 118 patients with melasma and 118 healthy controls analyzed the serum zinc level in patients with melasma compared with healthy subjects. Atomic absorption spectrophotometry was used to measure serum zinc levels. The mean serum zinc level in melasma patients and controls was 77.4 ± 23.2 μg/dL and 82.2 ± 23.9 μg/dL, respectively ($p=0.0001$). Serum zinc deficiency was found in 45.8% and 23.7% of melasma patients and controls, respectively. A positive family history of melasma in first-degree relatives was present in 46 (39%) of the cases, and a history of oral contraceptive pill use in 95 (81%) of the women with melasma. The aggravating factors for melasma were referred to as sun exposure (11.1%), pregnancy (15.3%), nutrition (2.5%), oral contraceptives (18.6%), and emotional stress (5.9%). Malar and facial patterns were observed in 3.4% and 72% of cases, respectively. Among patients with melasma, 20.3% had thyroid dysfunction, while in control subjects, 8.4% had thyroid dysfunction ($p=0.001$) **[14]**. In this regard, a review study provided an update on the clinical aspects, epidemiology, pathogenesis, and therapy of melasma and a perspective on future developments **[15]**.

## Skin, Melasma And COVID-19

The cutaneous manifestations of COVID-19 have been poorly described in a limited number of case reports. The first report of cutaneous manifestations related to COVID-19 showed that 18 of 88 COVID-19 positive patients (20.4%) developed cutaneous lesions **[16]**. A generalized macular or maculopapular rash was the most common skin manifestation, followed by chickenpox-like vesicles and cold urticaria **[17]**. These inflammatory lesions mainly occurred early in the course of the disease and were sometimes inaugural, preceding systemic infectious manifestations. Vascular lesions

including chilblains, livedo reticularis, non-necrotic and necrotic purpura have also been reported. Vascular lesions occurred later in the course of the disease, usually several days after the onset of general symptoms.

Despite this, little is known about the histology of these cutaneous manifestations. In addition, the mechanisms of cutaneous manifestations related to COVID-19 are not yet understood. It is unclear whether the skin symptoms are a secondary consequence of SARS-CoV-2 infection, a post-viral immune reaction, or a primary infection of the skin itself. Rashes can be induced directly by the virus, as is often seen in other viral illnesses. Furthermore, the difference in onset time between inflammatory and vascular lesions may indicate that these lesions have different origins **[18]**. To clarify the underlying mechanisms, large-scale prospective studies with biopsies, serological tests, and PCR analyzes of suspected patients are needed. Also, as SARS-CoV-2 infection led to asymptomatic cases for up to 14 days after infection, cutaneous manifestations can serve as a late indicator of infection, helping to provide a diagnosis **[19]**.

Besides, melasma is a common dermatological complaint, attributable to medication in up to 20% of all cases **[20]**. Many medications are associated with skin hyperpigmentation, such as non-steroidal anti-inflammatory agents, antihypertensive agents, antibiotics, and psychoactive agents **[21]**. In this sense, nephrotoxicity and neurotoxicity are common adverse reactions of polymyxin B, while skin hyperpigmentation has also been reported as a side effect recently **[22]**. Reports of cutaneous hyperpigmentation associated with polymyxin B in adults were rare, unlike in neonates **[23,24]**. Polymyxin B is mainly excreted by the kidney, requiring dose adjustment in patients with lower creatinine clearance **[25]**. Polymyxin B accumulation may be a possible reason for skin hyperpigmentation in neonates due to their immature renal function **[22,24]**.

Furthermore, polymyxin B-induced skin hyperpigmentation occurred mainly on the face and neck in most cases, while other parts of the body remained unchanged throughout treatment **[23,26,27]**. Sun exposure was excluded as a cause of skin hyperpigmentation, as exposed shoulders and arms were spared **[28]**.

Therefore, dermatological manifestations are rare in confirmed cases of COVID-19. Among 1,099 patients hospitalized with COVID-19 in Wuhan, only 0.2% had skin lesions **[29]**. There is no report so far about skin darkening associated with COVID-19. Maculopapular eruptions, pseudochills, and urticarial lesions are the most common cutaneous manifestations **[30]**. The trunk and extremities are the main areas involved and the lesions usually resolve spontaneously within a few days **[16,30]**. Therefore, skin hyperpigmentation (melasma) is unlikely to be caused by the new coronavirus **[28]**.

## Conclusion

Melasma is an acquired hyperpigmentation disorder, and reactive oxygen species play an important role in the regulation of melanin synthesis. In nutrological terms, lycopene is one of the most effective oxygen neutralizers among tomato-derived carotenoids. Furthermore, hydroquinone is a compound that has been used for the treatment of hyperpigmentation by tyrosinase inhibition mechanism and can be found in wheat. Thus, an adequate knowledge of the role of nutritional supplements in dermatological diseases can be a useful tool. Based on this, there is growing interest in oral medications and dietary supplements to improve melasma. Oral medications and dietary supplements evaluated include tranexamic acid, Polypodium leucotomos extract, beta-carotenoid, melatonin, and procyanidin. Also, hydrolyzed collagen is a low molecular weight protein that has been widely used and can prevent melasma. Serum zinc levels can also predict the occurrence of melasma. Finally, there is still no report on skin darkening associated with COVID-19.

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## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.



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