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Clinical Application of Kojic Acid in the Treatment of Melasma: A Scope Review

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Synopsis

Melasma is a pigmentary system failure marked by macules or symmetrically distributed irregular spots in sun-exposed areas, particularly on the forehead, lips, cheeks, and chin. With its ability to inhibit the tyrosinase enzyme, which is in charge of producing melanin, kojic acid (KA) is one of the depigmenting substances frequently employed in the topical treatment of melasma. This systematic scoping review followed the recommendations of Joanna Briggs and the *PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation* to map the therapeutic application of KA in treating melasma. The following databases, searched without regard to year or language through December 2022, were used: MEDLINE (PubMed), Embase, VHL, Scopus, Cochrane, Web of Science, and the grey literature. The search found 2,104 records in the databases. Eventually, 24 studies were added since they matched the requirements for eligibility. The outcomes and occurrences of adverse effects are influenced by variables such as the pharmaceutical form, concentration, frequency, period of treatments, and therapeutic associations. In the therapy of melasma, KA, whether isolated or associated, has substantial effects.

INTRODUCTION

Melasma, also known as acquired and chronic symmetrical cutaneous hyper melanosis, is a malfunction of the pigmentary system. It is recognized by macules or irregular spots on sun-exposed skin that range in tone from light brown to dark brown. It is distributed symmetrically, mostly throughout the parts of the face that include the chin, cheeks, lips, and forehead. Other body parts such as the neck and chest may be affected less frequently (1).

Melasma may develop due to exposure to ultraviolet radiation (UVA and UVB), sunlight, exposure to visible light, genetic predisposition, pregnancy, and exogenous hormone use. The use of various drugs such as anticonvulsants; photosensitizing cosmetics; nutritional inadequacy; and ovarian and thyroid dysfunction are other variables that may contribute to the development of melasma. Women with darker skin and those from Asian, Latin American, Middle Eastern, and African regions with higher sun exposure are most affected

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by this dysfunction. In addition, it significantly impacts the quality of life, resulting in psychological problems including depression and low self-esteem (2,3).

Histologically, melasma is characterized by an increase in melanin in the epidermis and dermis. Unfortunately, melasma's clinical course is sometimes lengthy, resistant to treatment, and typically recurs once treatment is stopped or with increasing sun exposure (3).

Current treatments include topical and systemic agents, chemical peels, laser, and light-based therapies. The goals of the treatment should be to improve existing lesions and avoid recurrences. Topical therapies include ultraviolet (UV) backlight protection, depigmenting agents, retinoids, corticosteroids, tranexamic acid (TXA), and combinations of these. Depigmenting or keratolytic topical medications include hydroquinone (HQ), tretinoin, azelaic acid, kojic acid (KA), niacinamide, and TXA, among a wide range of others. Glycolic acid (GA), salicylic acid (SA), and trichloroacetic acid (TCA) are three commonly utilized chemical peels. Intense pulsed light, Q-Switched ND YAG Laser (ADSS, Beijing, China), and fractional laser are a few examples of laser/light-based therapies. TXA and natural supplements are recent systemic medications. Melasma can be improved by combination therapy, which typically yields superior results (2,4).

Among the depigmenting substances commonly used in the topical treatment of melasma is KA, which may be applied alone or in combination with other substances or therapies. Also known as 5-hydroxy-2-hydroxymethyl-4-pyrone (International Union of Pure and Applied Chemistry, IUPAC), KA is a naturally occurring chemical produced when fungi such *as Aspergillus* and *Penicillium* ferment carbohydrates. Its function is to lighten the skin by inhibiting the tyrosinase enzyme, which is responsible for melanin production. Tyrosinase contains copper ions that regulate melanin synthesis by a two-step reaction. In the first stage, tyrosinase catalyzes tyrosine hydroxylation in L-3,4-dihydroxyphenylalanine (L-DOPA) and oxidation of DOPA in dopaquinone. In the second stage, dopaquinone converts into melanin. So, when tyrosinase is inhibited, melanin production is blocked, which leads to a decrease in pigment formation (5).

Due to its mechanism of action, KA has wide application in the cosmetic industry. With the growth of this industry, its supply and demand are increasing considerably, and clinical studies are essential for designing and developing new products based on KA (6,7). However, there needs to be more literature regarding the use of KA as a depigmenting agent in treating melasma. Publications of systematic and scoping reviews or other methodologies that gather primary studies on this asset were not found to evaluate the safety and efficacy alone or in association with other therapies.

This systematic scoping review aims to map the clinical application of KA in treating melasma by mapping the literature that is currently available. These publications provide a descriptive view of the pharmaceutical forms of KA as well as delivery, concentration, treatment duration, frequency of application, and associations. In addition, these publications summarize the evidence found on efficacy and safety, if available, regarding reducing the severity of melasma spots, improving the quality of life of carriers, and adverse effects reported.

METHODS

STUDY DESIGN

This scoping review was carried out following the guidelines of the Joanna Briggs Institute to map, describe, and categorize the available information on the clinical use of KA in the treatment of melasma (8).

The selection steps of the studies included in this review were performed according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation (9).

A previously developed protocol was made available under open access in the Open Science Framework repository (DOI 10.17605/OSF. IO/P7G6R <https://osf.io/f5dhk>), as well as complete data from the included studies.

INVOLVEMENT OF STAKEHOLDERS

This scoping review had the direct participation of a pharmaceutical aesthete (J.B.S.) and three specialists in cosmetology (V.E.B.C., E.P.S., Z.M.F.F.) in the refinement of the protocol and screening of the studies.

RESEARCH QUESTION

This scoping review was guided by the following question: How is the clinical application of KA in the treatment of melasma performed? To describe the pharmaceutical forms of delivery of KA, concentration, treatment duration time, frequency of application and associations, reduction of the severity of melasma spots, improvement of the quality of life of carriers, and adverse effects were reported.

The research question followed the acronym Population, Concept, and Context (PCC):

Population: Studies involving participants of both sexes, of any age, and with melasma who received melasma treatment through topical application of KA alone or in association with other actives or therapies. Studies involving participants with other pigmentation disorders were excluded.

Concept: This scoping review was based on the following main concepts: KA and melasma:

- KA, whose IUPAC name is 5-hydroxy-2-hydroxymethyl-4-pyrone, which is a substance of natural origin that is obtained from the fermentation of carbohydrates by fungi such as *Aspergillus* and *Penicillium.* Its function is to lighten the skin by being able to inhibit the enzyme tyrosinase, which is responsible for melanin production (5).
- Melasma, which is a dysfunction of the pigmentary system known as acquired and chronic symmetrical cutaneous hyper melanosis. It is characterized by macules or irregular spots of light brown to dark brown coloration in skin areas exposed to the sun. It is distributed symmetrically on areas of the face, such as the forehead, lips, cheeks, and chin. It may affect other body areas more rarely, such as the neck and chest (1).

Context: This review has no restrictions regarding the year of publication of the studies, country of origin, or place where these treatments were investigated.

The complete strategy for each database is described in Complementary File 1 (<https://osf.io/54nkw>). This was elaborated using the following terms: Medical Subject Headings (MeSH), Health Descriptors (DeCS), alternative terms, and keywords:

- MeSH: KA, Melanose, Adverse Effects;
- DeCS: Portuguese (Melanose, efeitos colaterais e reações adversas relacionadas a medicamentos) and English (Melanosis, Drug-Related Side Effects, and Adverse Reactions);
- Alternative terms for DeCS: Chloasma, Melasma, Adverse Effects, Adverse Event, Adverse Events;
- Keywords: KA, Melasma, Adverse Effects.

ELECTRONIC DATABASE FOR STUDY IDENTIFICATION

The following databases were consulted: MEDLINE (PubMed), Embase, VHL, Scopus, Cochrane Library, and Web of Science, without restricting year and language, through December 2022.

OTHER RESEARCH RESOURCES FOR IDENTIFYING STUDIES

The search strategy has been adapted to grey literature, including Google Scholar, Open Gray, the ISRCTN registry, ClinicalTrials, the Australian New Zealand Clinical Trials Registry, the International Clinical Trials Registry Platform operated by the World Health Organization, the EU Clinical Trials Register, the American Academy of Dermatology, the British Association of Dermatologists, the Annual Meeting of European Academy of Dermatology and Venereology, and the Annual Scientific Meeting of the Australasian College of Dermatologists.

Manual searches were also performed in the references of the included studies to find as much material as possible for this review.

ELIGIBILITY CRITERIA

The clinical application of KA either alone or in combination with the treatment of melasma in both primary and secondary studies.

EXCLUSION CRITERIA

Studies that included participants with pigmentation disorders other than melasma or who did not use KA as one of the therapies were excluded. In addition, *in vivo* and *in vitro* studies, literature reviews, and charts were excluded.

ELIGIBILITY DETERMINATION

References were managed and selected by Rayyan software (10), where duplicates were automatically removed. Two reviewers (R.V.B. and J.B.S.) independently evaluated the titles and abstracts to verify whether they met the eligibility criteria. Subsequently, a complete reading of the article was performed by the same reviewers, also independently, to confirm eligibility within the guidelines described above. Discrepancies were resolved by consensus by a third reviewer when necessary. Notably, the reviewers underwent a calibration process before determining eligibility.

DATA EXTRACTION

The data from the included studies were extracted independently by two reviewers (R.V.B. and J.B.S.). The information was organized in Microsoft Excel. The same reviewers performed the extraction of data independently. The discrepancies were resolved through

discussion and consensus. The reviews were calibrated by extracting at least three documents of different quality levels and reaching a consensus. This procedure was repeated until the reviewers could correctly extract and standardize the data. For this scoping review, the following data were extracted:

1. Study characteristics: country, study design, bibliometric information
2. Characteristics of the intervention: the pharmaceutical form of KA, concentration, treatment duration, frequency of application, and associations
3. Outcome characteristics: reduced melasma severity, improved quality of life, and adverse effects

RESULTS

The search was carried out in the data period and recovered 2,104 records. Of these, 562 were duplicated and removed, and 1,542 were screened by reading titles and abstracts. Of these, 50 were included for full-text reading. In total, 24 studies were included in this scoping review because they met the eligibility criteria. The study selection process is described in Figure 1:

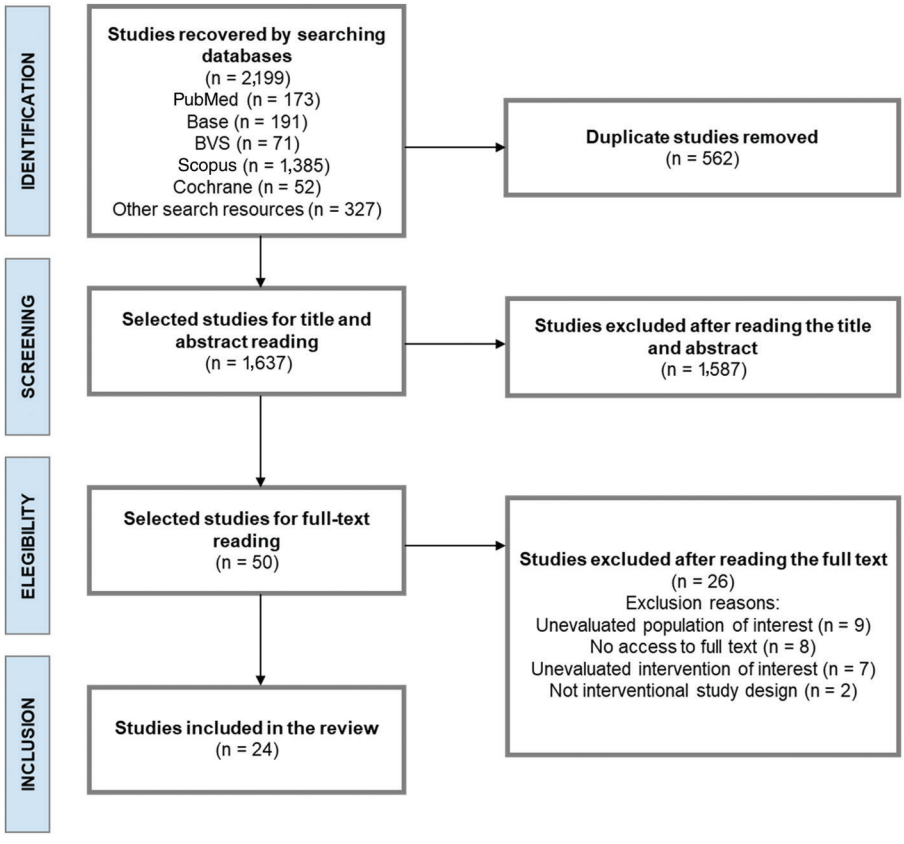


Figure I. Flowchart of the study selection process.

The studies showed patients of both sexes, but most were female, representing 69.3% of the population studied. Male patients represented 8.5%, and studies that did not specify the gender of the participants corresponded to 22.2%. The mean total age was 40 years old, with participants between 15 and 80 years. Regarding the design of the study, 10 were case reports and 14 were randomized clinical trials; of the latter, 3 studies were split-sided. Most of the studies included did not report or did not have funding. Only four studies declared funding, two by research institutions and two by industry. As for conflicts of interest, either they were not reported or there were none. The characteristics of the studies included in this review are described in Table I.

Since 1996, there have been one to two studies that have used KA alone or in combination with other agents or procedures in treating melasma; this number has been steady over time. Except for 2013 and 2021, there were three and four studies published, respectively. In 2022, no study was recovered through this scoping review. Graph 1 displays the studies included in this review in chronological order.

The origin of the studies included in this review corresponds to several countries, with an $n = 1$ (Singapore, Egypt, France, Bangladesh, China, Iran, Mexico, and Indonesia). Brazil, Portugal, and Pakistan verified an $n = 2$ for each one. The countries with the highest number of publications were Italy ($n = 3$), the United States ($n = 3$), and India ($n = 5$). Figure II illustrates the regional distribution of the studies that made up this scoping review.

Of the 24 studies included in this review, 4 used KA alone and 18 in combination. In two studies, KA was used in the isolated and associated forms. As for the pharmaceutical form, the cream was more described. The concentration of KA ranged from 0.75% to 10%. The mean treatment duration was 12 weeks, except in 4 studies, the study duration was 6 months, 2 months, 18 weeks, and 8 to 36 weeks. All of the investigations detailed a daily and nightly application schedule. The melasma area severity index (MASI) score was used in the majority of studies to demonstrate a significant decrease in melasma spots. Yet, only three studies reported an improvement in the participants' quality of life. Of the studies included, seven did not report adverse effects. Among the adverse effects, mild ones including erythema, burning, itching, and irritation were observed. In studies using isolated KA, the adverse effects reported were only erythema or redness, burning, itching, and dryness. The characteristics of the intervention regarding pharmaceutical forms of KA delivery, concentration, treatment duration, frequency of application, and adverse effects are described in Table II.

Among the leading associations of KA in the formulations used by the studies included in this review are AG, Arbutin, HQ, and vitamin C, followed by TXA, vitamin E, niacinamide, and HEPES. Graph II describes the correlation between the number of publications and the KA-related actives.

Adverse effects reported by the six studies that evaluated the use of KA alone in the treatment of melasma were described as erythema or redness ($n = 2$), burning ($n = 1$), itching ($n = 1$), dryness ($n = 1$), flaking ($n = 1$), and burning ($n = 2$). At the same time, two of these studies did not report the occurrence of adverse effects. The percentage corresponding to the occurrence of adverse effects related to the use of KA alone in the treatment of melasma is described in Graph III.

Table I
Characteristics of the Included Studies ($n=24$)

Author/year	Country	Study design	Sex	Age	Financing	Conflicts of interest
Sardesai *et al.*, 2013 (11)	India	Case series	F ($n=127$) M ($n=33$)	21–40 ($n=132$) <20 ($n=140$ >40 ($n=14$)	Not reported	Not reported
Monteiro *et al.*, 2013 (12)	India	Randomized clinical trial	F ($n=49$) M ($n=11$)	All ages	None	None
Cameli *et al.*, 2014 (13)	Italy	Case series	F ($n=50$)	28–40 ($n=22$) 41–50 ($n=25$) 51–62 ($n=3$)	None	None
Yenny, 2018 (14)	Indonesia	Randomized split-face clinical trial	F ($n=45$)	>18	Ministry of Research and Technology through DIPA Andalas University funding 2016	Not reported
Iraji *et al.*, 2014 (15)	Iran	Double-blind randomized clinical trial	F and M ($n=40$)	All ages	Not reported	Not reported
Sheikh *et al.*, 2021 (16)	Pakistan	Randomized clinical trial	F ($n=27$) M ($n=13$)	>18	Not reported	Not reported
Mesquita-Guimarães *et al.*, 2005 (17)	Portugal	Case series	F ($n=17$) M ($n=2$)	23–50	Not reported	Not reported

(*Continued*)

Table I
Characteristics of the Included Studies ($n = 24$)

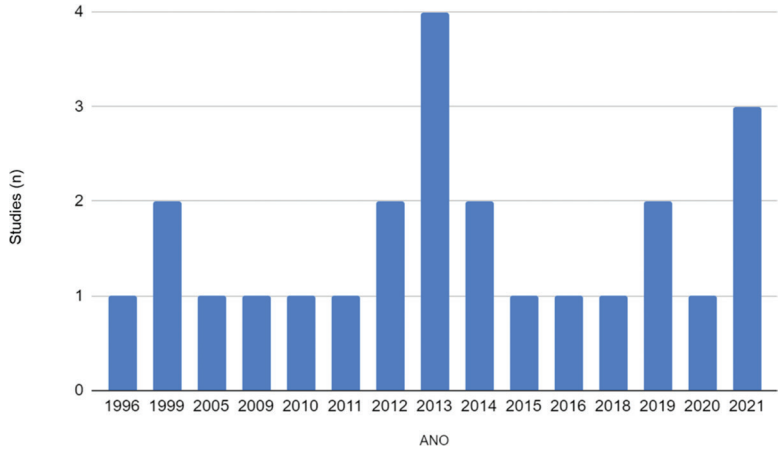
Author/year	Country	Study design	Sex	Age	Financing	Conflicts of interest
Azzam *et al.*, 2009 (18)	Egypt	Randomized clinical trial	F ($n = 45$)	24–50	Not reported	Not reported
Costa *et al.*, 2012 (19)	Brazil	Randomized clinical trial	F beginning ($n = 120$) end ($n = 102$)	18–50	Material supplied by Mantecorp Chemical and Mantecorp Skincare	None
Berardesca *et al.*, 2019 (20)	Italy	Case series	F ($n = 91$) M ($n = 9$)	>18	Relief Srl, Italy	None
Desai *et al.*, 2019 (2)	Brazil	Case series	F ($n = 55$)	27–60	Not reported	Not reported
Bhagwat *et al.*, 2016 (21)	Pakistan	Randomized clinical trial	F and M ($n = 60$)	18–45	Not reported	Not reported
Chowdhury *et al.*, 2012 (22)	Bangladesh	Case series	F and M ($n = 30$)	15–50	Not reported	Not reported
Fragoso-Covarrubias *et al.*, 2015 (23)	Mexico	Randomized clinical trial	F ($n = 63$)	29–59	Not reported	Not reported
Tsilika *et al.*, 2011 (24)	France	Case series	F ($n = 10$)	Not reported	Not reported	None
Xing *et al.*, 2021 (25)	China	Case series	F ($n = 26$) M ($n = 1$)	18–65	Natural Science Foundation of China and Shanghai Sailing Program	None

(*Continued*)

Table I
Characteristics of the Included Studies ($n = 24$)

Author/year	Country	Study design	Sex	Age	Financing	Conflicts of interest
Draelos *et al.*, 2010 (26)	United States	Randomized clinical trial	Unreported sex beginning ($n = 80$) end ($n = 79$)	25–60	Not reported	Not reported
Deo *et al.*, 2013 (27)	India	Simple randomized blind clinical trial	F ($n = 67$) M ($n = 13$)	18–58	Not reported	None
Arunnair *et al.*, 2021 (28)	India	Randomized clinical trial	F ($n = 71$) M ($n = 31$)	18–65	Not reported	Not reported
Garcia; Fulton, 1996 (29)	United States	Randomized split-face clinical trial	F ($n = 38$) M ($n = 1$)	24–80	Not reported	Not reported
Srivastava *et al.*, 2020 (30)	United States	Case series	F ($n = 6$)	36–59	Not reported	None
Cotellessa *et al.*,1999 (31)	Italy	Case series	F ($n = 36$) M ($n = 4$)	33–61	Not reported	Not reported
Lim *et al.*, 1999 (32)	Singapore	Randomized split-face clinical trial	F ($n = 40$)	32–58	Not reported	Not reported
Wali *et al.*, 2013 (33)	India	Randomized clinical trial	F and M ($n = 100$)	Not reported	Not reported	Not reported

F: female; M: male.



Graph I. Chronological distribution of the studies included in this review.

DISCUSSION

MAIN FINDINGS AND COMPARISON WITH THE LITERATURE

Kojic acid is a natural substance produced biologically by various fungi and bacteria during aerobic fermentation. It was discovered in Japan by Saito in 1907 from the fermentation of white rice (*koji* in Japanese), which gave rise to its name KA. In 1955 Charles Pfizer and Company in the United States announced the first attempt to manufacture this organic acid industrially; the company patented the production and recovery methods. Subsequently, with the growth of the cosmetics market, the use of KA commercially gained appreciation (7,34). This scoping review looked at the number of publications over the years involving isolated KA or in association with other actives or procedures in the treatment of melasma. It was observed by this scoping review that the number of studies did not decrease over time, even though this asset is not recent in the cosmetics field and has been studied in the treatment of melasma for more than 20 years. In 2013, publications reached their high and returned to growth in 2021.

Melasma is a common dyschromia with population prevalence that varies according to ethnic composition, skin phototype, and intensity of sun exposure. However, it was observed in this scoping review that the countries where the most studies occur are Italy, the United States, and India, where only the latter is related to greater sun exposure by the participants because of its tropical climate. In contrast, Italy and the United States have temperate climates with warmer temperatures and lower sun exposure. Another important observation is that only two of the publications included in this review came from Brazil, a tropical country where the prevalence of melasma can range from 5.9% to 9.1%, according to different regions of the country (35).

Of the 24 studies included in this review, 14 used MASI (*n*) or modified melasma area and severity index (mMASI) (*n*) as an instrument to measure the clinical response of the therapies submitted. Two studies used MI as a measure of pigment evaluation. Regarding assessing the quality of life, only three studies presented data using melasma quality of life scale (MELASQol) (2) or dermatology life quality index (DLQI) (1). On the other hand, seven studies did not describe a validated instrument or method to assess the clinical

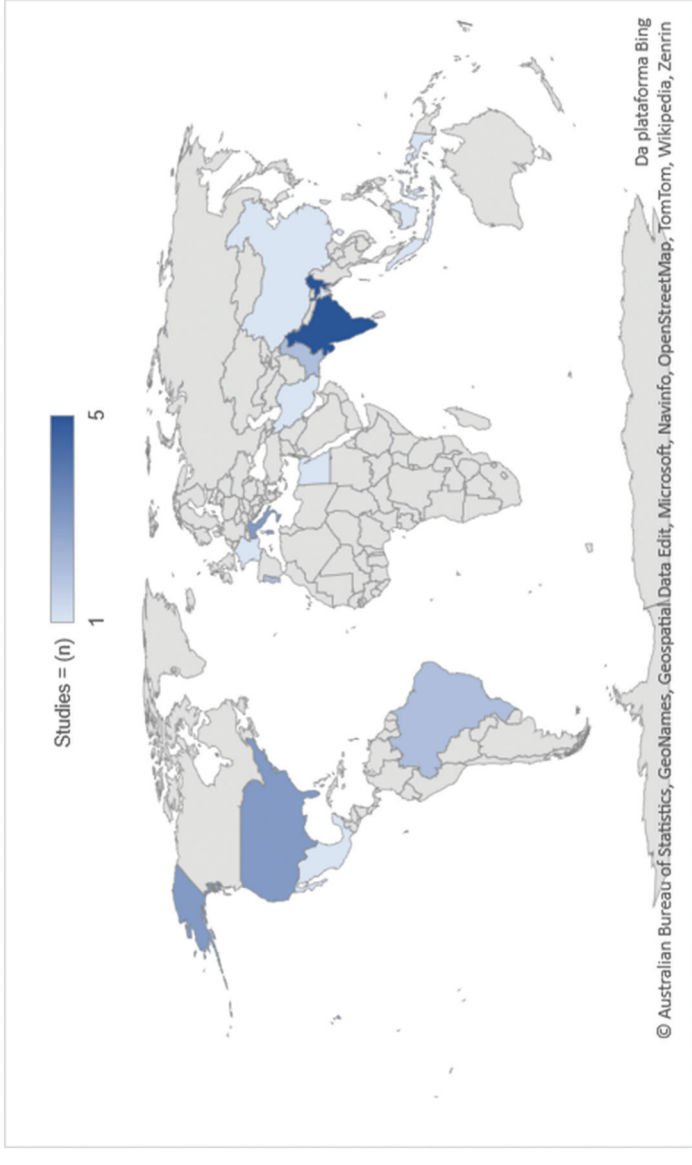


Figure II. Geographic distribution of the studies included in this scoping review.

Table II
Characteristics of the Intervention Regarding Pharmaceutical Forms of KA Delivery, Concentration, Treatment Time, and Frequency of Application

Author/year	Association/pharmaceutical form/concentration	Frequency of application/ treatment duration	Reduced severity of stains	Improving the quality of life	Adverse effect
Sardesai *et al.*, 2013 (11)	Group A: 3% KA and 2% vitamin C cream; Group B: 5% Arbutin, 10% GA, and 3% KA cream	Daily use, at night, for 3 months	In both groups, there was a statistically significant mean MASI score reduction. However, Group A showed a more significant improvement than Group B.	It does not apply	Group A: erythema and burning; Group B: erythema, burning, flaking, and itching
Monteiro *et al.*, 2013 (12)	0.75% KA and 2,5% vitamin C cream	Daily use, at night, for 12 weeks	The mean reduction of the MASI score was significant from week 0 to week 12 ($p \leq 0.001$). There was no significant change from week 0 to week 4 ($p = 0.121$), however from week 0 to week 8 there was a significant reduction ($p < 0.001$).	It does not apply	Erythema
Cameli *et al.*, 2014 (13)	1% KA, <1% uva-ursi, <1% arbutin, <1% pineapple, <1% green tea, <1% *Capparis spinosa* extract, <1% vitamin C palmitate, <1% papaya, and <1% aloe transdermal gel administered by monopolar radiofrequency (Phytogel)	Six sessions with an interval of 1 week. Patients were evaluated before treatment, after 1 month, and 6 months after treatment.	One month after the completion of treatment, the initial mean MASI score of 21.3 dropped to 15.7 ($p < 0.001$), and after 6 months of follow-up, the average value was 16.9. These results were confirmed by a statistically significant decrease in the mean melanin score recorded using a Mexameter in T1 (214.46) and in T2 (216.24) compared to baseline T0 (260.76) ($p < 0.001$).	It does not apply	It was not reported
Yenny, 2018 (14)	4% cream (left cheek)	Daily use, at night, for 12 weeks. The evaluation was performed every 2 weeks.	Week 0: left face MASI scores 11.7 Week 4: MASI scores 10.9 Week 8: MASI scores 9.9 Week 12: MASI scores 8.6	It does not apply	Redness, burning, and itching

(*Continued*)

Table II
Characteristics of the Intervention Regarding Pharmaceutical Forms of KA Delivery, Concentration, Treatment Time, and Frequency of Application

Author/year	Association/pharmaceutical form/concentration	Frequency of application/ treatment duration	Reduced severity of stains	Improving the quality of life	Adverse effect
Iraji *et al.*, 2014 (15)	2% KA cream	The treatment lasted 3 months. Patients were evaluated every month. Frequency of unreported application.	In total, 79% of patients were cured after 3 months. According to Friedman's test, regarding the time of pigment healing, there was a significant difference between the groups ($p = 0.008$). The two groups had a significant difference regarding pigment tone changes at the end of the second and third months.	It does not apply	It was not reported
Sheikh *et al.*, 2021 (16)	Group A: oral TXA capsules + KA cream Group B: KA cream	The study lasted 3 months. The patients were followed up in the eighth and 12th weeks. Frequency of unreported application	Group A: there was a significant decrease in the MASI score from 12.08 ± 2.8 to 9.1 ± 2.2 in the eighth week and from 8.2 ± 2.0 in the 12th week ($p < 0.05$ for both). Group B: MASI score decreased from 12.6 ± 2.4 to 10.9 ± 2.4 in the eighth week and then 10.3 ± 2.9 in the 12th week. In this group, the decrease in the MASI was significant in the eighth week, $p < 0.05$, and was insignificant in the 12th week, $p > 0.05$.	It does not apply	Group A: abdominal cramps and oligomenorrhea Group B: erythema and dryness
Mesquita-Guimarães *et al.*, 2005 (17)	10% GA, 3% KA, 2% arbutin, 2% depigmenting factor 174J/276-D, 2% octyl methoxycinnamate, 1% butyl methoxydibenzoylmethane, 0,3% titanium dioxide, 0,5% disodium EDTA, 0,15% vitamin E, and 0,2% alpha-bisabolol cream	Daily use in the morning and night for 12 weeks. The evaluations were performed in the fourth, eighth, and 12th weeks.	The extent of lesions decreased significantly from first to last consultations ($p = 0.001$), with 68.8% of patients having affected areas greater than 20 cm^2. Decrease in melasma area between consultations, predominantly in patients with initial area greater than 50cm^2. Only 3 patients (18.7%) still had their original area at week 12.	It does not apply	Local irritation, contact dermatitis, itching, erythema, shilling, and flaking

(*Continued*)

Table II
Characteristics of the Intervention Regarding Pharmaceutical Forms of KA Delivery, Concentration, Treatment Time, and Frequency of Application

Author/year	Association/pharmaceutical form/concentration	Frequency of application/ treatment duration	Reduced severity of stains	Improving the quality of life	Adverse effect
Azzam *et al.*, 2009 (18)	2% HQ and 2% KA cream	Daily use, at night, for 2 months.	The MASI score before treatment (mean ± SD = 14,500 ± 2.107) decreased significantly ($p < 0.001$) after treatment (mean ± SD = 8.327 ± 2.172) and at the end of the follow-up period (10.813 ± 1.778)	It does not apply	It was not reported
Costa *et al.*, 2012 (19)	KA, arbutin, Sepiwhite®, and Achromaxyl® cream	Daily use twice a day for 90 days. The evaluations took place every 30 days.	The initial mean MASI was 12.73 (D0), which went to 10.89 (D30) and 9.65 (D60), finishing the study with 8.63 (D90)	The mean MELASQol in D0 was 45.62; in D90 it was 27.09 ($p < 0.001$)	A: erythema, flaking, pinching, ardor, and flaking.
Berardesca *et al.*, 2019 (20)	KA and vitamin A cream (day)+KA and glycolic cream (*n*ight)	Daily use twice a day, morning and evening, for 90 days. The evaluations were made in the first week, then 45 days and 90 days after the start of treatment.	At 90 days, the mean MASI score for all patients was significantly lower than at baseline (−2.1; 1.128 ± 0.129 versus 3.29 ± 0.267, $p < 0.00001$). It is important to note that a statistically significant reduction in the mean score of the mMASI was also observed at 45 days (2.193 ± 0.181 versus 3.29 ± 0.267, $p < 0.0001$).	It does not apply	It has no adverse effects
Desai *et al.*, 2019 (2)	3% TXA, 1% KA, 5% niacinamide, and 5% HEPES sérum	Daily use twice a day, morning and evening, for 12 weeks. The evaluations were made in weeks 2, 4, 8, and 12.	At 4 weeks, there was a considerable decline in the melanin index (MI) scores of the lesional melasma skin. At week 8, the skin of lesional melasma showed a decrease in MI by up to 9%. The normal skin perilesional (control site) also showed an MI decrease at week 4.	It does not apply	Erythema or redness, itching, or burning

(*Continued*)

Table II
Characteristics of the Intervention Regarding Pharmaceutical Forms of KA Delivery, Concentration, Treatment Time, and Frequency of Application

Author/year	Association/pharmaceutical form/concentration	Frequency of application/ treatment duration	Reduced severity of stains	Improving the quality of life	Adverse effect
Bhagwat *et al.*, 2016 (21)	2% KA, octinoxate, and allantoin gel	Daily use, at night, for 3 months. The evaluations were performed every month for 3 months.	Initial mean (MASI0) MASI score of 10.02 ± 5.81. After completion of treatment, i.e., after 3 follow-ups (MASI3), the mean MASI score was 3.35 ± 4.25. The mean reduction in the MASI score was 6.67 (66.5%) at the end of treatment. The reduction in MASI was statistically highly significant ($p < 0.0001$).	It does not apply	It was not reported
Chowdhury *et al.*, 2012 (22)	HQ, KA, and GA	Daily use, at night, for 12 weeks.	The MASI score decreased by 24.20%, indicating a decrease in melasma severity according to the scale: 0 = no reduction; up to 25% = mild; 26–50% = moderate; above 50% = remarkable reduction	It does not apply	Itching, burning, flaking, and erythema
Fragoso-Covarrubias *et al.*, 2015 (23)	5% arbutine, 10% GA, and 2% KA cream	Daily use, at night, for 3 months.	At the beginning of the study, the MASI index was 10.68 ± 5.19 (limits: 4.6 and 21.7). It found an average reduction in the MASI index of 7.2 ± 4.22 (limits: 2.3 and 15). The initial and final MASI indexes had a significant difference ($p = 0.001$).	The mean MELASQoL score in patients was 40.18 ± 21.15 (limits: 7 and 67). The MELASQoL score until the end of the study was 33.12 ± 17.79 (limits: 2.3 and 56). When comparing the points of the MELASQoL indicator at the beginning and end of treatment, there was a significant reduction in treatment ($p = 0.001$).	Erythema, burning, and irritation

(*Continued*)

Table II
Characteristics of the Intervention Regarding Pharmaceutical Forms of KA Delivery, Concentration, Treatment Time, and Frequency of Application

Author/year	Association/pharmaceutical form/concentration	Frequency of application/ treatment duration	Reduced severity of stains	Improving the quality of life	Adverse effect
Tsilika *et al.*, 2011 (24)	Azelaic acid, KA, alpha arbutin, *Glycyrrhiza glabra* extract, and ascorbic acid cream	Daily use for 12 weeks. Patients were evaluated in the week that started, weeks 4, 8, 12, and at week 12 + 4.	Before treatment, the mean MASI score was 22. After completion of treatment, the MASI decreased to 11 ($p = 0.008$). Decrease in MASI after 1 month of treatment maintained up to 1 month after the end of the treatment.	It does not apply	Mild irritation
Xing *et al.*, 2021 (25)	3% TXA, 5% niacinamide, 1% KA, and 5% HEPES sérum	Daily use, twice a day, for 12 weeks. Patients were evaluated in the following weeks: 0.2, 4, 8, and 12.	Two weeks after treatment, mMASI scores decreased significantly ($p = 0.044$, which was very close to the cutoff value for significance of 0.05). At 4, 8, and 12 weeks, mMASI scores decreased significantly, indicating gradual improvement of melasma: 4 weeks ($p < 0.01$); 8 weeks ($p < 0.001$); 12 weeks ($p < 0.001$).	It does not apply	It was not reported
Draelos *et al.*, 2010 (26)	KA, emblica extract, and GA cream	Daily use, twice a day, for 12 weeks. Patients were evaluated at weeks 4, 8, and 12.	At week 8, a statistically significant improvement was observed for uniform tone ($p = 0.003$) and hyperpigmentation ($p = 0.007$). At week 12, a highly statistically significant improvement was observed for skin texture/softness, clarity, uniform tone, hyperpigmentation, brightness, and general appearance ($p = 0.001$) and the size of dark spots ($p = 0.021$) and in the intensity of dark spots ($p = 0.001$).	It does not apply	It was not reported

(*Continued*)

Table II
Characteristics of the Intervention Regarding Pharmaceutical Forms of KA Delivery, Concentration, Treatment Time, and Frequency of Application

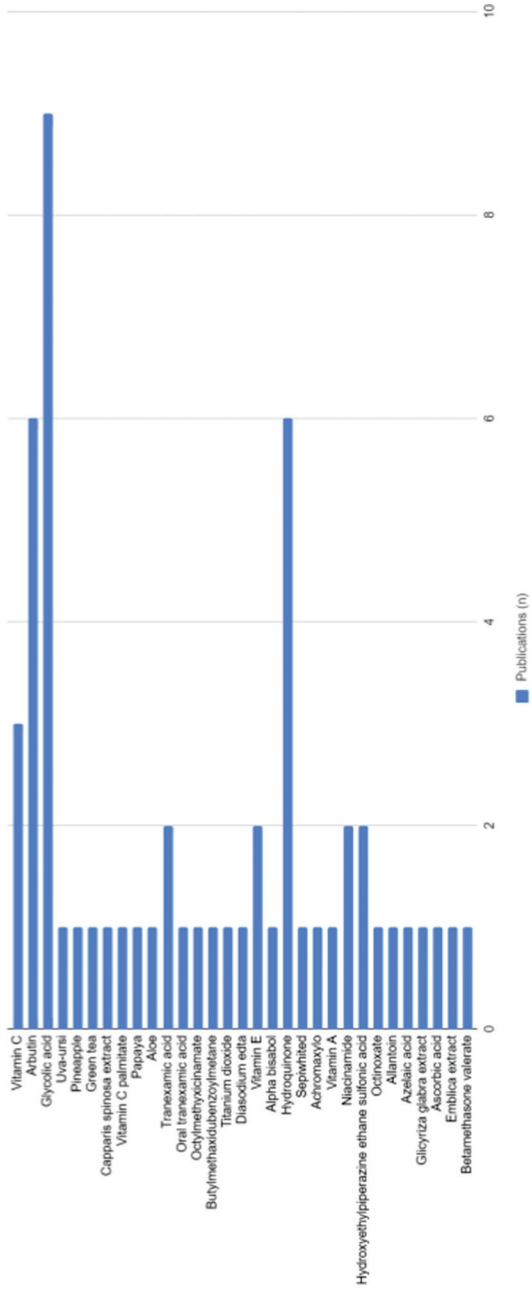
Author/year	Association/pharmaceutical form/concentration	Frequency of application/ treatment duration	Reduced severity of stains	Improving the quality of life	Adverse effect
Deo *et al.*, 2013 (27)	Group A: 1% KA cream Group B: 1% KA and 2% HQ cream Group C: 1% KA, and 0.1% betamethasone cream Group D: 1% KA, 2% HQ, and 0,1% betamethasone cream	Daily use, at night, for 12 weeks. Patients were evaluated at weeks 4, 8, and 12.	Group A: the mean percentage of improvement in the MASI score was 58.72% Group B: the mean percentage of improvement in the MASI score was 71.87%, with an excellent response at 60%, good at 30%, and regular and poor at 5% each Group C: showed the lowest improvement (36.46%) Group D: the mean percentage of improvement in the MASI score was 54.03%, with 25% showing excellent improvement, a good response at 35%, a reasonable at 35%, and a poor at 5%	It does not apply	A: burning B: burning C: it was not reported D: acneiform rashes
Arunnair *et al.*, 2021 (28)	HQ, KA, GA, and vitamin E cream	The treatment lasted 3 months, with three visits for follow-up. Frequency of unreported application.	It does not apply	The DLQI score at baseline was 9.65. On the first visit, there was a reduction of 7.84. On the second, it decreased to 5.75. And on the third visit, there was a reduction to 3.12. The DLQI scores from the beginning to the end of the study and from the beginning until each visit were significant with a $p < 0.01$.	Erythema, itching, irritation, and dryness of the skin

(*Continued*)

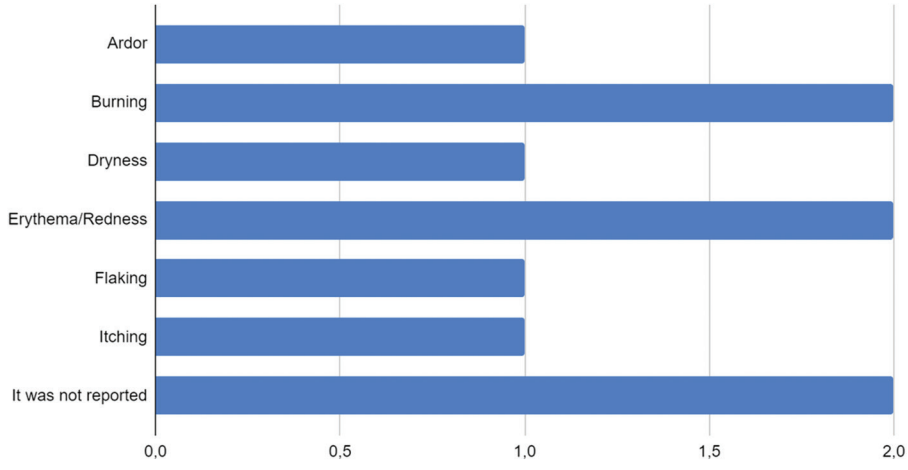
Table II
Characteristics of the Intervention Regarding Pharmaceutical Forms of KA Delivery, Concentration, Treatment Time, and Frequency of Application

Author/year	Association/pharmaceutical form/concentration	Frequency of application/ treatment duration	Reduced severity of stains	Improving the quality of life	Adverse effect
Garcia; Fulton Jr., 1996 (29)	KA gel (on only one side of the face)	Daily use, twice a day, for 3 months	28% of patients had an improvement with the use of KA. Note: the difference in pigment reduction between KA and HQ (comparator) was not significant ($p > 0.05$).	It does not apply	Burning and flaking
Srivastava *et al.*, 2020 (30)	12% HQ, 6% KA, and 5% vitamin C cream.	Treatment lasted from 8 to 36 weeks, varying between patients. Frequency of unreported application.	Before and after treatment, MASI scores decreased on average by 63.77 ± 22.10% ($p = 0.0002$)	It does not apply	Erythema, telangiectasia, atrophy, and flaking
Cotellessa *et al.*,1999 (31)	50% GA and 10% KA gel (peeling)	The sessions were held every 2 weeks for 3 to 6 months	30% of patients had a complete reduction of melasma, 60% had a partial reduction, and 10% of the patients had no reduction	It does not apply	Light erythema, light flaking
Lim *et al.*, 1999 (32)	2% KA, 10% GA, and 2% HQ gel. (on only one side of the face)	Daily use, twice a day, for 12 weeks. The evaluations were performed every 4 weeks.	Melasma improvement was observed in week 4 and continued throughout the study. Only two patients had their melasma gone, and more than half of the melasma was eliminated in 24 of 40 patients (or 60%).	It does not apply	Redness, burning, and light exfoliation
Wali *et al.*, 2013 (33)	KA cream	Daily use, at night. The patients were followed up during the third, sixth, and ninth weeks.	In 40% of the patients, there was a slight improvement. In 35%, there was a moderate improvement, which may be noticeable. In 20% there was an obvious improvement. And in 5% there was a very marked improvement.	It does not apply	It was not reported

DLQI: dermatology life quality index; EDTA: ethylenediamine tetraacetic acid; GA: glycolic acid; HQ: hydroquinone; HEPES: hydroxyethylpiperazine ethane sulfonic acid; KA: kojic acid; MASI: melasma area and severity index; mMASI: modified melasma area and severity index; MI: melanin index; MELASQol: melasma quality of life scale; TXA: tranexamic acid.



Graph II. Correlation between the number of publications and the KA-related actives in the treatment of melasma.



Graph III. Adverse effects related to the use of KA alone in the treatment of melasma.

response or quality of life. These data demonstrate the heterogeneity of scientific research in clinical trials or case reports related to aesthetic dysfunctions or dermatology. Even with validated and recommended evaluation instruments, some authors still need to use them to make their results more reliable and comparable.

The evaluation of melasma's clinical response may be correlated with pharmaceutical form, KA concentration, frequency of use, treatment duration, and therapeutic associations. In addition, the occurrence of adverse effects is also linked to the variation of these conditions.

Thus, in the studies that used KA in association with other actives or therapeutic resources, it is possible to observe that the lowest concentration of KA (0.75%) occurred when it was used in association with 2.5% vitamin C, presenting only erythema as an adverse effect. The mean reduction in the MASI score was significant from the first week of treatment to the end, in the 12th week (12). The erythema reported in addition to being related to KA may be related to vitamin C, since they are among the expected effects for its application as described since 1999 as ardor, erythema, and dry skin, easily treated with hydration (36).

On the other hand, no adverse effects were reported when the concentration of KA was 1% in association with monopolar radio frequency for transdermal administration of the gel formulation with diverse agents associated (uva-ursi, arbutin, antioxidant agents such as pineapple, green tea, *Capparis spinosa* extract, vitamin C palmitate, papaya, and aloe) and also by the cream formulation of 1% KA, 3% TXA, 5% niacinamide, 5% hydroxyethyl piperazine ethanerazazine (13,25). In the first study, a significant reduction in melasma can be observed where the MASI score decreases after the first month and 6 months after treatment. The same can be observed in the second study with a treatment period of 12 weeks, in which there was a significant reduction in the mMASI score since the beginning of treatment (13,25).

When the formulation of 1% KA, 3% TXA, 5% niacinamide, and 5% HEPES serum was used, the following adverse effects were presented: erythema, itching, redness, or burning. The treatment lasted 12 weeks and resulted in a significant reduction in melanin index (MI) scores. It is observed that the same concentration of previous studies and similar associations was used, but with different demonstrations of the occurrence of adverse effects (2).

In another study, 4 groups used 1% KA for 12 weeks. Adverse effects were grouped according to the association used. The 1% KA cream showed burning (Group A); 1% KA and 2% HQ creams showed burning (Group B); 1% KA, 2% HQ, and 0,1% betamethasone creams showed acneiform eruptions (Group C); and finally, 1% KA and 0,1% betamethasone creams were not reported to have an adverse effect (Group D). Group B had the best result in the mean reduction of MASI score, followed by groups A, D, and finally, group C. Thus, it is observed that even at low concentrations, i.e., up to 1%, KA presents significant results in reducing spots and with few mild adverse effects even when in association with other actives (27).

Some studies found no adverse effects even when 2% KA was administered and when used isolated could demonstrate the cure of 79% of patients after 3 months (15). Another study reported a significant MASI score reduction in 2 months of treatment with 2% KA and 2% HQ cream. In this last case, it is questionable that there haven't been any negative HQ-related adverse effects, although this could be observed because of the short treatment. The association of 2% KA with octinoxate and allantoin in the gel for 3 months of treatment described a statistically high and significant reduction in the MASI score (21).

Some adverse effects can be observed in other studies using a cream formulation of 2% KA in association with 5% arbutin and 10% AG, reporting effects such as erythema, burning, and irritation. Despite presenting adverse effects, there were satisfactory results in the MASI score and MELASQoL score, with a significant reduction from the beginning of treatment to the end, in 3 months (23). Effects such as redness, burning, and mild exfoliation were reported through a treatment that lasted 12 weeks with the gel formulation of 2% KA, 10% GA, and 2% HQ. It resulted in an improvement in melasma from the fourth week on, and two patients were eliminated. Over half of the melasma was eliminated in 60% of the patients (32). In these cases, clinical response and adverse effects may be linked to the combined actives. GA present in both studies has keratolytic action and can therefore generate more significant irritation and even exfoliation (37).

The study that used 3% KA and 2% vitamin C cream (Group A) and 3% KA, 5% arbutin, and 10% GA cream (Group B) experienced erythema and burning, while group B also observed flaking and itching as adverse effects. As an average reduction of the MASI score, group A had a more significant improvement than group B (11). The presence of more effects was observed in the studies conducted also using a cream formulation of 3% KA combined with 10% GA, 2% arbutin, 2% depigmenting factor 174J/276-D, 2% octyl metoxicinamate, 1% butyl metoxydubenzooilmethane, 0,3% titanium dioxide, 0,5% EDTA dianhydride, 0,15% vitamin E, and 0,2% alpha-bisabolol. There were observed adverse effects such as erythema, flaking, itching, local irritation, contact dermatitis, and xerosis. According to this study, the affected areas were significantly reduced from the initial assessment to the end of treatment, which was in the 12th week (17). Once again, adverse effects might be associated with other agents used in therapeutic combinations, including GA (37).

Employing a higher concentration of KA such as 6% with 12% HQ and 5% vitamin C, common unfavorable effects such as erythema and flaking were observed, as well as less common ones like telangiectasia and atrophy. Such effects might be expected due to the high concentration of components and the long treatment duration, which lasted about 8 to 36 weeks. The MASI mean was significantly reduced (30). In this situation, it would be crucial to compare the outcomes with those obtained with lower amounts. However, due to heterogeneity, such a comparison is unfeasible.

The highest concentration of KA was 10%. However, it was applied in peeling in association with 50% AG and in a gel formulation. For daily use, the highest concentration was 6%. It presented an adverse effect of mild erythema and mild flaking, expected by the high concentration of the agents used. The duration of treatment was 3 to 6 months, with application every 2 weeks, resulting in 30% of patients with complete reduction of melasma, 60% of patients with partial reduction, and 10% without any reduction of melasma. However, it was not using any validated instrument to evaluate this clinical response, so the results are subjective and cannot be compared to other studies (31).

In some studies, the concentrations of KA used were not reported. KA cream was associated with an oral TXA capsule and presented adverse effects such as abdominal cramps and oligomenorrhea, which are indeed related to oral treatment with TXA and unrelated to KA. To corroborate this explanation, in the same study, another group used isolated KA cream and related only erythema and dryness as adverse effects. The outcomes achieved considerably lowered the MASI score for both groups after 3 months of treatment. The improvement in the first group was higher due to the association with TXA. However, the cost-benefit of this association should be assessed due to the risk of systemic adverse effects (16).

Erythema was also one of the adverse effects found using KA, arbutin, Sepiwhite™, and Achromaxyl™ cream. The concentrations of the agents used were not reported. In addition to erythema, brushing, burning, and flaking were also reported. As a result of the MASI score and MELASQoL, they had a significant mean reduction during the 90 days of treatment (19). KA, HG, and GA creams were used, also without the concentration reported, and similar adverse effects such as erythema, flaking, burning, and itching were observed. After 12 weeks, a slight reduction in the MASI score occurred (22). Erythema, pruritus, irritation, and skin dryness were reported using KA, HQ, GA, and vitamin E creams. In this case, the DLQI score significantly reduced with each visit from the beginning of treatment until 3 months, which was the end of treatment, indicating an improvement in quality of life (28). When the application of KA gel was studied, adverse effects such as burning and flaking were observed within 3 months of treatment, and only 28% of patients had an improvement (29). Finally, mild irritation was reported with the formulation of KA, azelaic acid, alpha arbutin, *Glycyrrhiza glabra* extract, and ascorbic acid cream, and had a significant MASI score reduction after 1 month from the beginning of treatment and remained 1 month after the 12 weeks of treatment (24). A similar formulation of KA cream, emblica extract, and GA did not report adverse effects but showed a statistically significant improvement in uniform tone, texture, hyperpigmentation, brightness, size, and intensity (26).

In another study using KA cream isolated with unreported concentration, 40% of the patients had a slight improvement, 35% showed a moderate improvement and 20% had a noticeable improvement. There was a very marked improvement in 5% of these (26,33). Daytime use of KA and vitamin A cream, and night cream of KA and AG, showed no adverse effects over the 90 days of treatment and had a significant reduction in the MASI score and a mean mMASI (20).

Among the most described associations are GA (50% and 10%), Arbutin (5%, 2%, and 1%), HQ (12% and 2%), and vitamin C (5%, 2.5%, and 2%). Using KA with high concentrations and other substances showed promising results in reducing melasma. On the other hand, a higher occurrence of adverse effects was already predicted because each associated activity has several expected adverse effects.

Most of the studies described the daily nocturnal application, except for the studies that did not report the frequency of application (15,16,28,30). And when KA was associated with weekly radio frequency or applied as a peeling fortnightly (13,31). The duration of treatment, in general, was 12 weeks; 11 studies showed improvement in the reduction of spots by reducing the MASI score at the end of this period. In addition, six studies demonstrated improvement in the MASI score in the first weeks of treatment.

Hence, the claims of more significant adverse effects could be directly related to the increase in concentration. Only burning happened when KA was used at 1%; reports of redness, burning, and itching occurred when its concentration was increased to 4%. However, it is impossible to confirm this statistically since the included studies have low methodological quality and need to correctly describe the incidence of adverse effects. The improvement of melasma observed by all investigations independent of KA concentration is a crucial feature to take into account. However, more studies should be conducted with more homogeneous or standardized evaluation criteria to establish a proportionality relationship between MASI reduction.

STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of this scoping review include the high methodological rigor, the publication of a previous protocol, the use of explicit eligibility criteria, broad and complex research in databases and other records, and the selection and evaluation of studies by independent and standardized reviewers.

The studies included are a limiting factor for the results observed due to their methodological quality and heterogeneity in reporting the results of safety and efficacy. It is also worth mentioning that most studies did not consider the patient's quality of life as an evaluation of the participants, a critical outcome for this clinical condition. The findings related to the safety and efficacy of KA were similar to the previously published studies, suggesting, based on the available emerging evidence, that it may be safe and effective in treating melasma.

IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

The present scoping review observed the association of KA with several actives, but more was needed concerning its association with aesthetic procedures. Thus, the results gathered in this review can serve as a guide for new publications, generating new research questions and demonstrating where the limitations of studies already published are and, consequently, the knowledge about the clinical application of these formulations in treating melasma.

Other reviews available in the literature address the use of KA, but not when specifically used in the in-depth treatment of melasma, or approached through reviews without methodological rigor as a scoping or systematic review (4,7,38,39). This scoping review contributes as a guide to the clinical application of KA by presenting results of several studies published over more than 20 years, which demonstrate that the application of KA alone or in therapeutic association produces significant results in reducing the severity of spots and improving the quality of life associated with melasma. Thus, it can guide the prescription of concentrations, treatment duration, and associations according to the results presented and the adverse effects reported.

CONCLUSION

Using KA alone or in a therapeutic combination significantly reduces the severity of spots and improves the quality of life associated with melasma. Even though it presents good results when used in isolation, the association with GA, arbutin, HQ, and vitamin C generates more promising results. The pharmaceutical form and frequency of application are well elucidated for gel, cream, or serum for nocturnal application. In addition, treatment should be continuous, as melasma tends to go into remission. The KA concentration has not been established because it was reported from 0.75% to 6% for daily application. Further studies should be carefully elaborated using all specific analysis methods for melasma, MASI, mMASI, MI, and MELASQol, generating robustness and comparability among clinical trials.

AUTHOR CONTRIBUTIONS

Rayane Vieira Brasil: conceptualization, methodology, software, investigation, data curation, writing—original draft preparation, formal analysis, writing—reviewing and editing; **Jenifer Brasil dos Santos:** conceptualization, methodology, software, investigation, data curation, writing—original draft preparation, formal analysis, writing—reviewing and editing; **Vânia Emerich Bucco de Campos:** methodology, investigation, supervision, validation, writing—reviewing and editing; **Elisabete Pereira dos Santos:** conceptualization, investigation, writing—original draft preparation, writing—reviewing and editing; **Zaida Maria Faria de Freitas:** project administration, methodology, investigation, data curation, supervision, validation, formal analysis, writing—reviewing and editing.

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Supplementary Material 1.
PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	2–3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a web address); and if available, provide registration information, including the registration number.	3
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5–6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	None
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6

(*Continued*)

Supplementary Material 1.
PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	6–7
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7–10
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	None
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	10–23
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	10–23
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	23–28
Limitations	20	Discuss the limitations of the scoping review process.	28
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	29
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	29

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

*Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and websites.

†A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4,5) refer to the process of data extraction in a scoping review as data charting.

§The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D *et al.* PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* 2018;169:467–473. doi: 10.7326/M18-0850.

Supplementary Material 2.
Detailed search strategy.

Electronic database and other research resources	Search strategy
MEDLINE (PubMed)	("kojic acid"[All Fields]) AND ("melanosis"[MeSH Terms] OR "melanosis"[All Fields] OR "melasma"[All Fields] OR "Chloasma"[All Fields]) ("kojic acid"[All Fields]) AND ("adverse effects"[MeSH Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR "Drug-Related Side Effects and Adverse Reactions"[All Fields])
BVS	"kojic acid" AND (melasma OR chloasma OR melanosis) "kojic acid" AND ("adverse effects" OR "adverse event" OR "adverse drug reaction")
Embase	("kojic acid" OR (kojic AND ("acid"/exp OR acid) AND ("chloasma"/exp OR chloasma) AND ("melanosis"/exp OR melanosis) "kojic acid" AND ("adverse event" OR "adverse drug reaction")
Escopus	"kojic acid" AND (melasma OR chloasma OR melanosis) "kojic acid" AND ("adverse effects" OR "adverse event" OR "adverse drug reaction")
Cochrane Library	Kojic acid AND Melasma Kojic acid Melasma
Google Scholar, Open Gray, the ISRCTN registry, ClinicalTrials, the Australian New Zealand Clinical Trials Registry, the World Health Organization International Clinical Trials Registry Platform, the EU Clinical Trials Register, the American Academy of Dermatology, the British Association of Dermatologists, the European Academy of Dermatology Annual Meeting, and the Annual Meeting of the Australasian College of Dermatologists	Kojic acid AND Melasma Kojic acid Melasma

Supplementary Material 3
List of reasons for the exclusion of studies, after reading them in full ($n = 18$).

Author/Year	Title	Exclusion reasons
Truchuelo; Jimenez; Jaen, 2014	Assessment of the efficacy and tolerance of a new combination of retinoids and depigmenting agents in the treatment of melasma.	Unevaluated intervention of interest.
Iurassich; Santoro; Rossi, 2010	A case of chemical vitiligo due to kojic acid.	Unevaluated population of interest.
Tejera-Vaquerizo; García-Gavín, 2019	Allergic contact dermatitis due to kojic acid.	Unevaluated population of interest
Serra-Baldrich; Tribô; Camarasa, 2007	Allergic contact dermatitis from kojic acid.	Unevaluated population of interest.
Ikeno, 2000	Clinical evaluation of a cream containing kojic acid and licorice extract on hyperpigmentation of the skin.	No access to full text.
Harada, 2000	Clinical evaluation of whitening cream containing kojic acid and oil-soluble licorice extract for senile pigment fleckle on the face.	Unevaluated population of interest.
Oresajo; Yatskayer, 2009	Comparative evaluation for the efficacy and tolerance of two skin products containing either hydroquinone or emblica extract with kojic acid in female subjects with facial dyschromia.	Unevaluated population of interest.
Nakagawa; Kawai; Kawai, 1995	Contact allergy to kojic acid in skin care products.	Unevaluated population of interest.
Gold; Biron, 2011,	Efficacy of a novel hydroquinone-free skin-brightening cream in patients with melasma.	Unevaluated intervention of interest.
Park *et al.*, 2021	Evaluating the tolerance and efficacy of laser-assisted delivery of tranexamic acid, niacinamide, and kojic acid for melasma: A single center, prospective, split-face trial.	No access to full text.
Al-Dhalimi; Yasser, 2021	Evaluation of the efficacy of fractional erbium-doped yttrium aluminum garnet laser-assisted drug delivery of kojic acid in the treatment of melasma: A split face, comparative clinical study.	No access to full text.
Burnett *et al.*, 2010	Final report of the safety assessment of kojic acid as used in cosmetics.	Not interventional study design.
Cotellessa *et al.*, 1999	Glycolic acid and kojic acid: A new combined treatment.	No access to full text.
Madhogaria; Ahmed, 2010	Leucoderma after use of a skin-lightening cream containing kojic dipalmitate, liquorice root extract and Mitracarpus scaber extract.	Unevaluated intervention of interest.

(*Continued*)

Supplementary Material 3
List of reasons for the exclusion of studies, after reading them in full ($n = 18$).

Author/Year	Title	Exclusion reasons
Hifuka *et al.*, 2015	Mixture of kojic acid and liquiritin cream for the treatment of various pigmentary disorders.	No access to full text.
Adatto, 2003	Photorejuvenation of the forearms by treating hyperpigmented lesions with intense pulsed light source: A case report.	Unevaluated population of interest.
García-Gavín *et al.*, 2010	Pigmented contact dermatitis due to kojic acid: A paradoxical side effect of a skin lightener.	Unevaluated population of interest.
Ellis; Tan; Ellis, 1995	Superficial micropeels: Glycolic acid and alpha-hydroxy acid with kojic acid.	Not interventional study design.
Nakayama *et al.*, 1994	The effect of kojic acid application on various facial pigmentary disorders.	No access to full text.
Mpofana; Abrahamse, 2018,	The management of melasma on skin types V and VI using light emitting diode treatment.	Unevaluated population of interest.
Iurassich; Blanco; Rossi, 1996	The treatment of melasma: Hydroquinone, liquorice extract and kojic acid. Clinical and colorimetric evaluation.	No access to full text.
Rendon; Bernitez, 2005	Use of a triple-combination agent and various procedures for treatment of melasma.	No access to full text.
Rendon, 2004	Utilizing combination therapy to optimize melasma outcomes.	Unevaluated intervention of interest.
Ashi; Kothiwhala, 2019	A 36-year-old woman with hyperpigmented macules on face.	Unevaluated intervention of interest.
Mamatha; Hanamanthayya, 2015	Comparative study on combination of microdermabrasion with 35% glycolic acid peel versus 35% glycolic acid peel alone for facial melanoses of Indian.	Unevaluated intervention of interest.
Sundaram, 2020	Prospective evaluation of efficacy and tolerability in skin phototypes IV to VI of a topical formulation for hyperpigmentation combining tranexamic acid with niacinamide, kojic acid, and hydroxyethylpiperazine ethane.	Unevaluated intervention of interest.