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Review Article

Kojic Acid in Dermatology: A Promising Approach for Melasma Treatment

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ABSTRACT

Melasma is a common dermatological condition characterized by brownish to grayish patches on the face, often associated with significant psychosocial and emotional distress. If left untreated, melasma can adversely affect the patient's quality of life. The etiology of melasma is multifactorial, involving hormonal changes, genetic predisposition, and environmental factors, with ultraviolet (UV) radiation being a key contributor through oxidative stress and melanocyte activation. Current treatment options, including hydroquinone, retinoids, corticosteroids, chemical peels, and laser therapies, provide varying degrees of efficacy, but none offer a complete cure for all patients. Therefore, there is a growing interest in discovering novel therapeutic agents, particularly from natural sources. Kojic acid, a naturally occurring compound produced by certain fungi such as Aspergillus oryzae, has gained attention in both medical and cosmetic applications for melasma management. It exhibits favorable bioavailability, therapeutic potential, and depigmenting effects. Preclinical and clinical studies have demonstrated its promising role as a primary treatment option for melasma, although certain limitations related to formulation and therapeutic effectiveness are being actively addressed. This review aims to comprehensively discuss the applications of kojic acid in melasma treatment, highlighting its advantages, limitations, and potential directions for future research.

INTRODUCTION

Melasma is a common skin condition that causes brown to grayish patches of skin to get darker and more unevenly formed on both sides of the face [1]. The parts of the body most affected are those exposed to the sun, such as the face, forehead, cheeks, and upper lip. Melasma happens when melanocytes make too much melanin [2]. This can occurdue to factors such as genetic, hormonal, and environmental causes, with UV light being a significant contributor. Even though melasma is not harmful, the fact that it is visible can have a significant impact on a person's mental and social health. Melasma mostly affects women, with a ratio of about 9 women to 1 man. It is also more common in people with darker skin types [3]. Depending on the population investigated and where it is located, the disease is present in 1% to 50% of people around the world. Regions with a lot of UV exposure, such as Latin America, Asia, and the Middle East, have higher rates of incidence [4]. For example, research shows that 8.8% of Hispanic people and up to 40% of

pregnant women in some areas have it, where it is sometimes called chloasma. Genetic predisposition, hormonal changes, and long-term solar exposure are all risk factors that make melanocyte activity worse [3].

Melasma's apparent nature has a significant effect on quality of life, often causing mental pain, low self-esteem, and social anxiety. Patients usually say they feel embarrassed or frustrated since the disease is so noticeable on their face, which is a big part of who they are and how they interact with others. Melasma's continuous and recurring nature makes these impacts much worse, since patients may have trouble managing it over the long term and deal with societal stigma. Because melasma has several causes and recurrences, it is still hard to treat. Hydroquinone, retinoids, corticosteroids, chemical peels, and laser treatments are some examples of topical medications that don't always work the same way [5]. Hydroquinone is considered the most effective treatment; however, it can cause side effects, such as itching and ochronosis, after prolonged use [6]. Azelaic acid and tranexamic acid are two other medications that show potential, although they don't work the same way for everyone. Recurrence is a significant problem, particularly when sun exposure is poorly controlled, as UV radiation can rapidly trigger melanogenesis again. Also, melasma is a long-term condition that requires ongoing treatment, which can be challenging for patients. These problems show the importance of finding new, safe, and effective treatments. Kojic acid may be a good option because it inhibits tyrosinase and has a good safety record.

Kojic acid (5-hydroxy-2-(hydroxymethyl)-4-pyrone) (Figure 1) is a chemical that occurs naturally in some fungi, especially Aspergillus oryzae, which is used to ferment foods like soy sauce, sake, and miso [7]. It is a result of fungal metabolism and is used in skin care because it can lighten dark spots. A lot of people choose it to treat hyperpigmentation problems like melasma because it comes from natural sources and is thought to be safe. The main reason why kojic acid works on melasma is that it can block tyrosinase, which is the main enzyme that makes melanin in skin cells [8]. Kojic acid binds to the copper ions in the active site of tyrosinase, further slowing down the production of melanin. This helps to lighten the skin over time. As a result, it is now a popular part of creams, gels, and serums for the skin. Kojic acid works better when mixed with other chemicals, such as hydrocortisone, according to research.

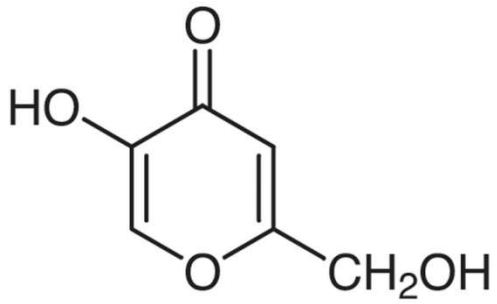

Figure 1: Structure of Kojic acid

This review examines existing research and clinical evidence to determine if kojic acid could be an effective treatment for melasma. It also looked at how it does this. This review examined the effects of kojic acids both individually and in combination with other chemicals. Lastly, we want to stress how important it is to do further research on this topic and how well patients can handle these kinds of products.

METHODOLOGY

This narrative review employed a critical search strategy using keywords such as kojic acid, melasma, skin depigmentation, and clinical use. The keywords were searched in databases such as PubMed, Google Scholar, and Scopus. Articles were selected based on their relevance to the topic. Data were extracted from published research papers, review articles, theses, book chapters, and books. Moreover, additional resources such as seminar reports and expert reviews have also been used for a comprehensive search. A total of 120 papers were screened, and out of these, 40 papers were used for the data synthesis.

Etiology And Pathophysiology Of Melasma

The etiology of melasma is complex, including multiple genetic, physiological, and environmental factors. These factors collectively contribute to excessive production of melanin. UV light is the primary factor that contributes to melanin production through the mechanism by which cells produce α-melanocyte-stimulating hormone, which in turn binds to melanocyte receptors and promotes tyrosine synthesis via p53 gene expression [2]. Another mechanism involved in melasma and UV radiation is the production of reactive oxygen molecules, which damage DNA and activate melanocytes, the cells responsible for producing melanin. This turns on critical signaling pathways, including MAPK and cAMP, which increase the production of tyrosinase

and other enzymes that help make melanin [9]. This produces more melanin, leading to the darker spots visible in melasma.

Female hormones play a vital role in melasma. Studies have shown that the symptoms of melasma worsen when the levels of estrogen and progesterone are high. It is usually seen in such a situation when the patient is pregnant, while taking birth control pills, or while undergoing hormone therapy. These hormones make melanocytes, which make pigment, work harder and enhance tyrosinase activity, which makes more melanin [10]. Genetics also plays an essential role in melasma. Familial clustering and specific polymorphisms in melanogenesis-related genes, such as microphthalmia-associated transcription factor (MITF) and tyrosinase (TYR), increase susceptibility towards melasma [11]. People with medium to dark skin tones (which are common in Asian, Hispanic, and African populations) are especially at risk since their skin naturally has more active pigment-producing cells.Apart from this, diseases such as thyroid problems, drug intake that makes people more sensitive to the sun, and the use of cosmetic products, all of which can lead to excessive melanin production or disrupt the skin's equilibrium.

Tyrosinase is an enzyme that helps turn tyrosine (an amino acid) into melanin. It is responsible for this overproduction. Tyrosinase that works too hard produces excessive pigment, which is subsequently passed on to surrounding skin cells (keratinocytes). This is what makes the dark spots in melasma. These patches can show up on the top layers of skin (epidermal melasma), the deeper layers (dermal melasma), or both (mixed melasma). It gets worse when in the sun because UV rays cause reactive oxygen species (ROS) to be released, which increases tyrosinase activity and helps transport pigment from melanocytes to nearby cells. Hormones, especially estrogen and progesterone, also play a role by making melanocytes more active and boosting the production of tyrosinase. This is why melasma is common during pregnancy or while using birth control (Figure 2).

Melasma is not just about color; it also has to do with blood vessels and inflammation. VEGF causes too many blood vessels to develop, while low-level inflammation (with molecules like IL-1 and IL-6) keeps melanocytes working too hard.Mast cells, which are a type of immune cell, may also help by releasing chemicals that make more melanin. When melasma is worse, pigment can leak into the lower layers of skin, where it is absorbed by specific cells called melanophages. Also, fibroblasts, which are skin cells, send out signals (such SCF and HGF) that make melanocytes even more active [12].

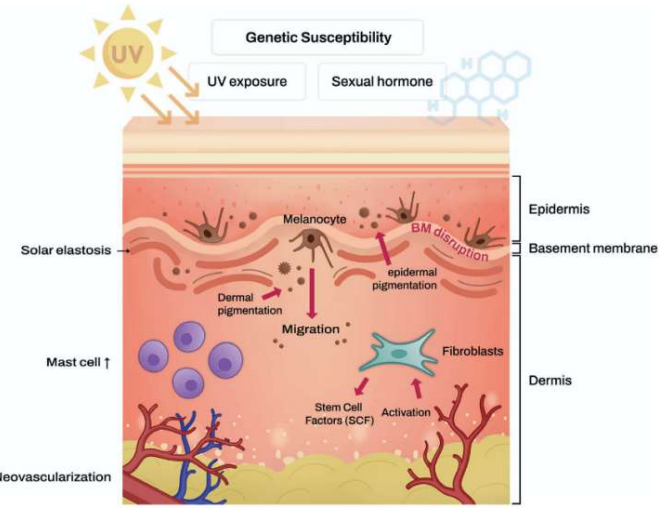

Figure 2: Pathogenesis of Melasma. The figure was adopted from a published manuscript [13] under by-nc/4.0.

Kojic Acid: Properties And Mechanisms

Kojic acid is primarily produced by various fungi, notably Aspergillus oryzae, which is widely used in Asian cuisine for fermenting rice to produce sake and other traditional foods. The compound was first discovered in 1907 during studies on the fermentation process involving steamed rice and the koji mold, which inspired its name [14]. It has a wide range of applications across cosmetics, healthcare, pharmaceuticals, and even industry. Its most recognized role is in skincare, where it is used as a skin-lightening ingredient in creams, serums, lotions, soaps, and cleansers. Inhibiting melanin production helps address hyperpigmentation, dark spots, melasma, sun damage, and other forms of discoloration, resulting in a more even skin tone and a reduction in visible signs of aging [15].

Beyond its depigmenting effect, kojic acid also exhibits antioxidant, antimicrobial, and antifungal properties [16]. These activities make it useful in managing bacterial and fungal skin infections, supporting acne prevention, and improving overall skin health. Its applications extend beyond cosmetics: it is used in food preservation to prevent enzymatic browning, in medicine as a chemosensitizer to boost the activity of antifungal drugs, and in the development of radio-protective, anti-inflammatory, analgesic, and dental formulations. Additionally, it plays a broad role in agriculture and pest control,

serving as a component of insecticides, pesticides, and anti-parasitic agents.

Mechanism Of Action

Kojic Acid and Tyrosinase Inhibition

Kojic acid acts as a well-known inhibitor of tyrosinase, the key enzyme in melanin biosynthesis that determines pigmentation in the skin, hair, and eyes. Tyrosinase normally catalyzes two critical reactions: the hydroxylation of monophenols such as L-tyrosine into o-diphenols, and the subsequent oxidation of o-diphenols into o-quinones, which then polymerize to form melanin [17]. By interfering with these reactions, kojic acid effectively reduces melanin production.

The primary action of kojic acid is the competitive inhibition of tyrosinase monophenolase activity. It competes with the natural substrate L-tyrosine for binding at the enzyme's active site, preventing the initiation of melanin synthesis. A critical factor in this inhibitory mechanism is kojic acid's ability to chelate copper ions located at the enzyme's active site. Since tyrosinase requires two copper ions for its catalytic function, kojic acid binding effectively blocks substrate access and halts enzymatic oxidation. This copper-chelating property is central to its strong antimelanogenicactivity [18].
In addition to monophenolase inhibition, kojic acid also exerts a mixed inhibitory effect on the diphenolase activity of tyrosinase. This activity, responsible for oxidizing o-diphenols like L-DOPA to o-quinones, is suppressed by a combination of competitive and non-competitive interactions. As a result, both substrate binding and enzyme efficiency are reduced at this stage of melanin formation [17].

Kojic Acid and Antioxidant properties

Oxidative stress plays a critical role in its pathogenesis, with reactive oxygen species (ROS) generated from ultraviolet (UV) radiation, environmental pollutants, and inflammatory processes contributing to melanocyte stimulation and melanin overproduction. In this context, kojic acid has gained significant attention not only for its melanin-suppressing capabilities but also for its antioxidant properties that aid in skin protection.

Kojic acid acts as a chelating agent by binding metal ions, particularly copper and iron, which catalyze free radical formation through Fenton and Haber–Weiss reactions. By sequestering these metals, kojic acid limits the generation of ROS, thereby mitigating oxidative damage to cellular components such as lipids, proteins, and nucleic acids. This protective mechanism is essential in preventing further melanocyte activation and excessive pigmentation seen in melasma. Kojic acid exhibits the ability to neutralize free radicals directly. This scavenging activity helps in reducing oxidative stress within the skin cells, thereby protecting them from damage that could lead to inflammation and hyperpigmentation. Oxidative stress contributes to collagen breakdown, leading to skin aging and barrier dysfunction. By reducing ROS, kojic acid helps preserve collagen structure and function, which is crucial in maintaining skin elasticity and preventing the exacerbation of melasma. A study had demonstrated that a 3% kojic acid formulation significantly reduced skin discoloration, increased skin brightness, and improved skin homogeneity in 75% of patients with post-acne hyperpigmentation. These effects were attributed to the antioxidant properties of kojic acid, which helped in reducing oxidative stress and subsequent melanogenesis.

Pharmacokinetics of Kojic Acid: Skin Penetration and Bioavailability

The therapeutic efficacy of kojic acid in treating melasma is largely attributed to its ability to permeate the skin and exert its pharmacological action at the target site. As a small molecule (about 142.11 g/mol) with the ability to mix with water, kojic acid can penetrate the skin's outer layers fairly easily [19]. But the stratum corneum, that tough, outermost skin barrier,can make it complicated for it to reach deeper layers where it's needed most. Scientists have studied how kojic acid gets absorbed and spreads in the skin, and a lot depends on its chemical makeup and how it's formulated. Things like the type of cream, gel, or emulsion it's mixed into can make a big difference by softening up the stratum corneum or tweaking its lipid structure to let the molecule pass through more easily [20]. Adding penetration boosters like propylene glycol or urea, or even using carriers like liposomes or lipid nanoparticles, helps it sink in deeper and stick around longer, giving it a better shot at working [19].

Once kojic acid penetrates the skin, its bioavailability, which refers to the extent and distribution of the active compound, is influenced by multiple factors [21]. It tends to suspend in the epidermis, which is great since that's where melanocytes, the cells that make melanin, live. But it

can get cleared out quickly through things like water loss from the skin or broken down by enzymes like oxidases and hydrolases. To keep it stable, formulations often include antioxidants or other stabilizers. Research shows that 1–2% kojic acid is usually enough to block tyrosinase, the enzyme behind melanin production, without irritating the skin too much [18]. Higher doses might get more of the stuff in there, but could also cause more side effects. Getting the balance right with smart formulations is key to making sure kojic acid reaches those melanocytes in the lower epidermis and keeps working to manage melasma safely and effectively.

Evidence of Kojic Acid in Melasma Treatment

Preclinical Studies

Preclinical investigations into kojic acid's potential for treating melasma primarily revolve around its role as a tyrosinase inhibitor, which disrupts melanin synthesis in models of hyperpigmentation (Table 1). Although melasma is a human-specific disorder characterized by epidermal and dermal melanin deposition, these studies utilize in vitro enzyme assays, cell culture systems, and animal models of UV-induced pigmentation to infer efficacy. The evidence highlights kojic acid's anti-melanogenic properties, often compared to or enhanced through derivatives, supporting its mechanistic relevance to melasma management.

Several in vitro studies have elucidated kojic acid's mechanism as a tyrosinase inhibitor, a key enzyme in melanogenesis implicated in melasma pathogenesis. For instance, kojic acid was shown to act as a slow-binding inhibitor of tyrosinase's catecholase activity, forming an enzyme-inhibitor complex that undergoes a slow, reversible reaction, leading to time-dependent inhibition of melanin precursor oxidation. This non-classical inhibition underscores its potential to reduce hyperpigmentation by targeting tyrosinase directly [22].Derivatives of kojic acid have been synthesized to improve upon its inhibitory potency. Novel kojic acid derivatives demonstrated superior tyrosinase inhibition compared to kojic acid itself, with one compound (IIId) exhibiting an IC50 of 0.216 ± 0.009 mM through mixed-type inhibition and copper chelation at the enzyme's active site. Similarly, kojic acid derivatives linked to aminopyridine moieties showed potent uncompetitive inhibition, with the most active derivative (4h) displaying strong binding affinity via docking and molecular dynamics simulations, suggesting enhanced control over melanogenesis pathways relevant to melasma. In another series, kojic acid-coumarin derivatives exhibited excellent anti-tyrosinase activity, with compound 6f achieving an IC50 of 0.88 ± 0.10 μM as a mixed inhibitor, altering the enzyme's secondary structure and hydrophobicity. These findings position kojic acid and its derivatives as promising agents for hyperpigmentation disorders like melasma, though direct melasma models are absent [23-25].

In cellular models of hyperpigmentation, kojic acid has been tested in melanocytes to assess its depigmenting effects. In α-MSH-stimulated B16F1 mouse melanoma cells, kojic acid and its esters (monooleate, monolaurate, and monopalmitate) reduced tyrosinase activity and melanin content dose-dependently at nontoxic concentrations (1.95-62.5 μg/mL), with monopalmitate showing slightly superior melanin inhibition. Additionally, these compounds displayed antioxidant activity, potentially augmenting depigmentation by mitigating oxidative stress, a factor in melasma. The lower cytotoxicity of esters compared to kojic acid at higher doses suggests they could offer safer alternatives for treating melanin overproduction [26].

Animal models simulating UV-induced hyperpigmentation provide in vivo evidence for kojic acid's efficacy, mimicking solar triggers of melasma. In chronically UV-irradiated hairless mice, topical 1% kojic acid prevented epidermal hyperplasia, dermal fibrosis, and extracellular matrix increases via iron chelation, which may indirectly reduce oxidative damage and melanin synthesis associated with photodamage. Although direct melanin measurements were not emphasized, the anti-photodamage effects imply benefits for hyperpigmented conditions [27].

Overall, these preclinical studies affirm kojic acid's tyrosinase-inhibitory and antioxidant mechanisms in hyperpigmentation models, providing a foundation for its application in melasma treatment. However, the reliance on derivatives in recent works highlights opportunities for optimization to enhance potency and safety.

Clinical studies

Clinical evaluations of kojic acid (KA) for melasma treatment have primarily involved randomized controlled trials (RCTs) assessing its efficacy as a topical tyrosinase inhibitor, often in monotherapy or combination with agents like hydroquinone (HQ), glycolic acid (GA), or vitamin C. These studies typically measure outcomes using the

Melasma Area and Severity Index (MASI) or modified MASI (mMASI), clinical photography, and patient-reported assessments, with durations ranging from 12 to 16 weeks. While KA demonstrates depigmenting effects, it is generally less potent than HQ but offers better tolerability, making it suitable for long-term use or in patients with HQ sensitivity.

Randomized controlled trials have been evaluated earlier. For instance, in a prospective comparative RCT involving 60 patients with facial melasma, participants were randomized to receive either 4% HQ or 0.75% KA cream (with 2.5% vitamin C) applied nightly for 12 weeks. Both agents significantly reduced MASI scores ($P < 0.001$), but HQ showed superior efficacy with faster improvement (mean MASI reduction: 7.55 ± 5.29 vs. 4.99 ± 3.89 for KA at week 12); side effects like erythema were minimal and insignificant in both groups [28]. In another single-blind RCT with 80 adults diagnosed with melasma, participants were randomized into four groups: 1% KA alone, 1% KA + 2% HQ, 1% KA + 0.1% betamethasone valerate, or all three combined, applied nightly for 12 weeks. The KA + HQ combination yielded the highest mean MASI improvement (71.87%), outperforming KA monotherapy (58.72%) and other groups; adverse effects were rare, with only mild burning in a few cases across groups [29].In a split-face RCT of 39 patients with facial hyperpigmentation (including melasma), one side received 2% KA + 5% GA and the other 2% HQ + 5% GA for an unspecified duration. Equal pigment reduction was observed in 51% of patients, with KA superior in 28% and HQ in 21%, indicating comparable efficacy [8].

Combination therapy trials have also been evaluated as part of clinical studies. For example,in a split-face, evaluator-blinded RCT with 30 patients with mild-to-moderate melasma, one side received 5% alpha-arbutin + 2% KA cream and the other a triple combination cream (4% HQ, 0.05% tretinoin, 0.01% fluocinolone) for 12 weeks. Both achieved similar mMASI reductions (approximately 40-42%), but the KA combination had lower recurrence (10% vs. 25%) and fewer adverse events like erythema (13% vs. 30%)(30).Overall, these clinical studies support KA's role in melasma management, particularly in combinations, with consistent MASI improvements and low adverse event rates. However, larger, long-term trials are needed to optimize formulations and compare against emerging therapies.

Challenges And Limitations

Despite its widespread use as an effective depigmenting agent, kojic acid faces several challenges and limitations that affect its overall clinical utility in the treatment of melasma. One of the primary concerns is its instability in topical formulations, as kojic acid is prone to degradation when exposed to light, heat, and air, which can reduce its efficacy and increase the risk of skin irritation. To overcome these issues, stabilizers and advanced delivery systems such as liposomes and nanotechnology-based formulations have been developed [19]. Liposomes, for example, encapsulate kojic acid, protecting it from environmental stressors while enhancing skin penetration. Similarly, nanoemulsions and other nanocarriers improve their stability and bioavailability. At the same time, derivatives like kojic acid dipalmitate (KADP) offer enhanced lipophilicity and better skin absorption compared to the parent compound [32]. In addition to formulation challenges, clinical limitations such as variability in patient response also affect treatment outcomes. Factors like the severity of pigmentation, concurrent topical therapies, and patient adherence can result in inconsistent responses to kojic acid-based treatments [33]. Addressing these formulation, clinical, and patient-related limitations is essential to optimize the therapeutic potential of kojic acid and ensure its safe and effective use in managing melasma.

CONCLUSION

Melasma is a chronic condition that is challenging to treat due to its multifactorial etiology. So far, research and trials have demonstrated that kojic acid can be one of the best candidates to treat melasma by reducing the pigmentation, inhibiting tyrosinase, and activating the antioxidant mechanism. It is safe and tolerable, as demonstrated through clinical trials. However, its applications in melasma are limited due to physicochemical properties such as solubility, bioavailability, and formulation stability. Research has been ongoing to overcome its limitations and make it an ideal choice in the treatment of melasma.

SUMMARY

Melasma is a common chronic pigmentation disorder, mainly affecting sun-exposed facial regions and often leading to psychosocial distress. Its pathogenesis is multifactorial, involving genetic predisposition, hormonal influences, and ultraviolet (UV)-induced oxidative stress. Current therapies such as

Table 1: Studies carried out with kojic acid on melasma

Study Type	Model/Design	Key Findings	References
Preclinical (In Vitro Enzyme)	Polyphenol oxidase inhibition assays.	Competitive inhibitor via copper chelation, reducing melanin synthesis.	[31]
Preclinical (In Vitro Enzyme)	Tyrosinase catecholase activity assays.	Slow-binding inhibitor, time-dependent reduction in melanin precursor oxidation.	[22]
Preclinical (Cell Culture)	α-MSH-stimulated B16F1 mouse melanoma cells.	Dose-dependent reduction in tyrosinase activity and melanin content without cytotoxicity.	[26]
Preclinical (In Vitro Enzyme)	Mushroom tyrosinase assays with aminopyridine derivatives.	Potent inhibition (IC50 as low as 0.78 μM vs. kojic acid 18.25 μM); docking confirmed copper binding.	[23]
Preclinical (In Vitro Enzyme)	Mushroom tyrosinase anti-browning assays with derivatives.	Excellent inhibition (IC50 0.08-0.35 mM vs. kojic acid 0.42 mM); mixed-type with copper chelation.	[25]
Preclinical (Animal Model)	UV-irradiated hairless mice.	Prevented wrinkle formation and dermal alterations via iron chelation; implied depigmentation.	[27]

hydroquinone, retinoids, corticosteroids, chemical peels, and lasers show inconsistent results with high recurrence rates and potential side effects. Kojic acid, a natural fungal metabolite from Aspergillus oryzae, has emerged as a promising alternative due to its ability to inhibit tyrosinase through copper chelation and reduce oxidative stress via antioxidant activity. Preclinical studies highlight its potent anti-melanogenic effects, while clinical trials confirm efficacy both as monotherapy and in combination with other agents, demonstrating favorable safety and tolerability. Despite challenges of instability, limited bioavailability, and variable patient responses, advances in nanotechnology-based formulations and stable derivatives enhance its therapeutic potential. Kojic acid thus represents a safe, effective, and evolving strategy for melasma management.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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None

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