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Comprehensive Review of Kojic Acid and Its Derivatives: Biological Activities, Safety, and Therapeutic Potential in Depigmentation

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Abstract

There are several uses for kojic acid in human medicine, particularly in depigmentation. Additionally, derivatives of it are suggested to enhance efficacy, avoid side effects, and stop chemical degradation. With an eye toward human use and an attempt to clarify the action mechanisms, the goal of this study was to review the most recent scientific literature regarding the biological activities and safety information of kojic acid or its derivatives. During the evaluation of three distinct databases, the terms "toxicity," "adverse effect," "efficacy," "effect," "activity," and "safety" were crossed with the word "kojic." Articles were chosen based on predetermined standards. In addition to its depigmenting properties, kojic acid and its derivatives have antitumor properties and can function as antioxidants, antimicrobials, anti-inflammatories, radioprotectors, anticonvulsants, and agents for managing obesity. Following cell penetration, the molecules bind to the active site of tyrosinase, regulating factors involved in melanogenesis, modulating leucocytes, and scavenging free radicals, which results in depigmenting activity. As a result, ligands, size, and polarity all play significant roles in activity. Certain cancerous cell lines, such as those from melanoma, ovarian, breast, colon, and hepatocellular carcinomas, are susceptible to the cytotoxicity of kojic acid and its derivatives. In terms of safety, at the tested concentrations, kojic acid or its derivatives are safe compounds for human use. Applications in medicine, pharmacology, and cosmetics could benefit greatly from kojic acid and its derivatives.

Keywords: Kojic acid, activity, effect, action, safety, depigmentation

INTRODUCTION

First isolated in 1907, kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) is an organic acid that is produced by fermenting fungi of various genera, including Aspergillus and Penicillium [1]. Due primarily to its ability to inhibit tyrosinase, the primary enzyme involved in the synthesis of melanin, it is most frequently used as a skin depigmenting agent. Jomic acid depigmenting also involves leucocyte modulation, copper-chelating action, and free radical scavenging. In addition, reports of anti-inflammatory, antibacterial, and antioxidant properties were made [2]. Since the 1940s, antimicrobial and toxicity studies have been reported, but the mechanisms of action remain unclear.

In addition, many patents pertaining to kojic acid or its derivatives have been filed, either in relation to the manufacturing of the substance or to its application in medicine and cosmetics. A 1987 patent study revealed the synergistic effects of hydroquinone and kojic acid, specifically in terms

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of anti-inflammatory or depigmenting effects [3]. Furthermore, antidermatophytic, antimycobacterial, antityrosinase, and antioxidant properties of Mannich bases derived from kojic acid were demonstrated in a 2016 patent study [4]. Even with the large number of registers that go back to the 1950s,15, one can still find new patent documents in the modern era.

Kojic acid was usefully used to prepare over 150 different kojic acid derivatives because it is freely soluble in water, ethanol, acetone, or ethyl acetate. Some of these derivatives even represented previously unresearched chemical individuals. In order to predict the properties of new derivatives and to gather information for the investigation of the quantitative structure-time-activity relationships, physicochemical properties (hydrophobicity, acidity, and metal complexing ability) that are anticipated to be important in the biological activity of kojic acid derivatives were determined for a reasonable number of compounds using quantitative structure-time-activity relationship methods (QSTAR) [5].

KOJIC ACID DERIVATIVES AND NANOCARRIERS

Studies comparing the stability of kojic acid derivatives with kojic acid were not found, even though increased stability is one of the primary justifications for the use of kojic acid derivatives or for the incorporation of kojic acid into nanosystems. Stability studies were conducted in four studies involving kojic acid and nanotechnology [6]. In two of them, kojic acid was employed in nanoemulsions containing kojic monooleate, an ester made from kojic acid [7]. In a third study, kojic acid was employed in gelatinized core liposomes and a nanostructured lipid nanocarrier [8]. The nanoformulations were not compared to unencapsulated kojic acid or kojic monooleate in any of the studies. At least ninety days were spent on stability studies, during which samples were exposed to a range of temperatures, from four to forty-five degrees Celsius. Samples were deemed stable for the duration and conditions tested based on the evaluation of particle size, zeta potential, and polydispersity index. The entrapment efficiency was also assessed by Khezri and colleagues (2021) [6] and Ezzat and colleagues (2021) [8], who found no appreciable change (Table 1).

Table 1. Selected studies, with the molecules studied, activities/safety issues tested, and main conclusions related to kojic acid or derivatives.

Activity Evaluation	Safety Evaluation	Molecule	Main Conclusion Related to Kojic Acid and Derivatives
Anti-inflammatory	In vitro evaluation of cell viability using primary human monocytes	Kojic acid	Kojic acid in conc. of 50 µg/ml was able to induce morphological and phenotypical alterations in monocytes. Concentrations up to 100 µg/ml were not cytotoxic.
Skin depigmenting agent – Tyrosinase	Not evaluated	Kojic Acid	Kojic acid inhibited tyrosinase activity.
inhibitor and melanin synthesis inhibitor			and suppressed melanin synthesis. The IC50 inhibition values of mushroom, B16-4A5, and HMV-II tyrosinases were 297.4, 57.8, and 223.8 µM, respectively.
Pancreatic lipase inhibitor	Not evaluated	Kojic Acid	Kojic acid showed promising activity as an obesity management drug. It inhibited the pancreatic lipase enzyme with an IC50 of 6.62 µg/ml.
Radioprotector	In vitro evaluation of cell viability using CHO cells	Kojic Acid	Kojic acid has a radioprotector effect without causing cellular damage in concentrations under 100 µg/ml.

MAIN ACTIVITIES OF KOJIC ACID AND DERIVATIVES FOR HUMAN USE

Depigmenting Activity

Tyrosinase is an essential enzyme for the synthesis of melanin, and its inhibition is the primary mechanism underlying depigmenting activity. Tyrosinase's substrate is copper, which is chelated in the enzyme's active site by kojic acid. This prevents DOPA from tautomerizing into 5,6-dihydroxyindol-2-carboxylic acid. The kojic acid depigmenting mechanism also involves leucocyte modulation and free radical scavenging. In addition to tyrosinase inhibition in vitro from human and mushroom sources,

melanin content assessment in cells is widely used as an in vitro depigmenting technique. A few studies assessed kojic acid and/or its derivatives using both techniques (tyrosinase inhibition and melanin content) [9]. Tests on benzoate ester derivatives revealed that while compounds lacking an adamantane moiety inhibited the activity of mushroom tyrosinase but did not inhibit the synthesis of melanin, those containing such a moiety did the opposite. This observation is likely due, in part, to the variations in the amino acid sequences of murine and mushroom tyrosinases, as well as the mechanism underlying the depigmenting activity resulting from the presence of the adamantane moiety. In 2015, Kai et al. investigated the tyrosinase inhibitory effect of kojic acid on the tyrosinase content of mushrooms and the amount of melanin present in mouse melanoma cells (B16-4A5) and human melanoma cells (HMV-II). The concentration-dependent suppression of melanogenesis was observed at concentrations between 125 and 1000 μM of kojic acid, which may have its effect on tyrosinase inhibition in human cells. The IC50 inhibition value for HMV-II was 223.8 μM (Lajis et al., 2012). Using mouse B16F1 melanoma cells and mushroom tyrosinase, kojic acid esters were evaluated for tyrosinase activity and contrasted with kojic acid. The kojic acid esters were not substantially different from kojic acid in either type of enzyme; the results regarding melanin content were comparable to those of tyrosinase inhibition [10]. When tested by Mel-Ab cells and mushroom tyrosinase, kojic acid-phenylalanine amide and its metal complex had a greater depigmenting effect than the kojic acid molecule.

Antioxidant Activity

Because of its antioxidant activity, kojic acid and its derivatives prevent skin aging and inhibit melanogenesis, which makes them useful for treating skin disorders in the dermatological and cosmetic fields. Nine authors report this kind of activity for either kojic acid or its derivatives. When standard antioxidant tests like the hydrogen peroxide scavenging assay and the DPPH-free radical scavenging assay were used, kojic acid and its derivatives showed encouraging antioxidant activity. Of those, four investigations also documented the tested molecules' anti-melanogenesis activity, and Lajis and colleagues [10] connected the production of melanin with the existence of reactive species and free radicals. Thus, kojic acid's antioxidant properties would also be involved in regulating the synthesis of melanin.

Kojic dipalmitate, an esterified form of kojic acid, was employed in several emulsions by Gonçalez and colleagues. The multiple emulsion with kojic dipalmitate was found to be able to maintain the antioxidant activity more efficiently than the unencapsulated kojic dipalmitate when results from both were compared over the course of the experiment (28 days) [11]. Lobato and colleagues employed the methylation of kojic acid as a strategy. Using structural and electronic property analysis and density functional theory, the antioxidant activity of kojic acid and its methylated derivatives was assessed and compared to that of maltol and allomaltol. Higher antioxidant activity was the result of methylation [12].

Antitumor Activity

It has been reported that derivatives of kojic acid exhibit antitumor activity against various cancer cell lines. Malignant melanoma, ovarian cancer, breast cancer, colon cancer, and hepatocellular carcinoma were the cancerous cell lines that were examined. Studies have shown that derivatives of kojic acid are used to test new compounds or to increase the stability, effects, and reduction of the original molecule. Kojic acid derivatives can be used in a variety of ways to produce antitumoral activity; additionally, derivatives can aid in directing the molecule to the intended location within the human body. Depending on the properties of the cells, various mechanisms may be involved in the death of cancerous cells by kojic acid derivatives.

Derivatives of kojic acid were more potent than FDA-approved medications, except for vemurafenib, and cytotoxic against human malignant melanoma cell lines A375. The non-cancerous cell lines tested had higher IC50s (half maximal inhibitory concentration). According to the same study, certain compounds can prevent melanoma cells from producing melanin by inhibiting melanogenesis. To increase the concentration of intracellular ROS in the HEPG2 hepatocellular carcinoma cell line,

derivatives of kojic acid initiate an intrinsic p53 apoptotic pathway. By activating caspase 3/7 because of the derivatives' mitochondrial actions, apoptosis was inevitable. Utilizing VC-8-BRCA and VC-8 (ovarian cancer cell lines), the antitumor activity of kojic acid metal complexes was investigated. By adopting conformations and guiding the molecule to the desired binding site, metal complexes have the potential to improve the pharmacological uptake of drugs. To prevent DNA synthesis, kojic acid metal complexes were able to attach to the DNA of ovarian cancer cell lines. To test kojic acid derivatives antitumor activity, two distinct breast cancer cell lines – MCF-7 and MDA-MB-231 – were employed. Based on the properties of the cell line, it is proposed that the lipophilic derivatives will act in two distinct ways after passively penetrating the cancerous cell membrane. Necrosis was the reason behind the MDA-MB-231 cell line's death. Cell death resulted from the compound's oxidative stress and increased LDH activity [13].

Other Activities

Kojic acid and its derivatives have also been shown to have anti-senescence effects on.

Corneal Cells

Kojic acid has been shown to have anti-senescence activity for human corneal endothelial and epithelial cells, suggesting that it may be useful in the treatment of corneal injuries. Senescence is a normal aspect of aging, and as a result, alterations to the cornea are linked to a reduction in visual acuity. Thus, it is crucial to develop anti-senescence medications that stimulate cell division. According to a proposed mechanism, the downregulation of the related proteins galectin-8 and laminins occurs in endothelial cells through the transcription factor NF-κB and p-21 signaling pathways [14]. Regarding epithelial cells, it is hypothesized that kojic acid's anti-senescence mechanism promotes cellular proliferation by downregulating the expression of galectin8, ki67, and p-21 and increasing p-38 signaling [13].

Anticonvulsant

The study investigated the anticonvulsant properties of twelve kojic acid derivatives, also known as Mannich bases of kojic acid or allomaltol. The male mice used in the in vivo model were used to induce seizures using either maximal electroshock or subcutaneous Metrazol. Since kojic acid contains hydrogen bonds, it is hypothesized that the hydrogen bonds in its structure are related to the significant anticonvulsant activity exhibited by most derivatives [15].

Radioprotective

In terms of its radioprotective properties, kojic acid works to shield white blood cells, hemoglobin, and red blood cells. In male C57BL/6 mice, gamma-irradiation caused haematological parameters to decline; however, treatment with a single subcutaneous administration of 75 mg/kg or 300 mg/kg of kojic acid restored these parameters to their normal index, demonstrating protective activity. Furthermore, kojic acid can shield mice from gamma-irradiation-induced anemia [16].

MECHANISM OF ACTION OF KOJIC ACID

One type of secondary metabolite is KA, whose biosynthesis pathway is still unknown. On the other hand, it is claimed to chelate divalent ions and have tyrosinase and free radical scavenger properties. It functions by chelating copper (Cu+) at the tyrosinase enzyme's active site. Tyrosinase, also referred to as polyphenol oxidase, is the enzyme that converts L-tyrosine to L-3–4 L-3,4-dihydroxyphenylalanine and sets a limit on the rate at which melanin is synthesized. It is a member of the type 3 copper-containing protein family, and the active site contains two copper ions, Cua and Cub. CuA and CUB catalyze the oxidation of the o-diphenols to the resulting o-quinone derivatives (Diphenolase Activity) after they have converted monophenols (such as tyrosine) into o-diphenols (Monophenolase Activity). (Figure 1).

Based on the stage at which melanin production is disrupted, low-pigmenting agents can be broadly categorized. If the agents can act prior to, during, or after melanin production, that will determine the outcome. By acting as a sufficient inhibitor of monophenolase activity and a variable inhibitor of mushroom tyrosinase's diphenolase activity, KA functions during the actual synthesis of melanin.

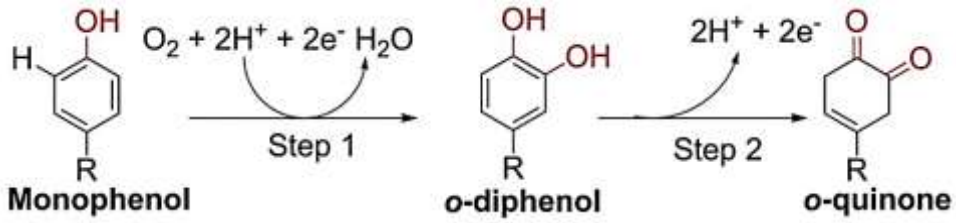

Figure 1. The reaction catalyzed by tyrosinase.

Assays for Evaluating the Efficacy of Kojic Acid

Numerous approaches, ranging from in vitro tests to in vivo and clinical investigations, can be used to evaluate the effectiveness of KA. Any of these approaches can occasionally result in false positives and false negatives, and they all have benefits and drawbacks.

The outcomes of earlier research on the effectiveness of KA in the management or treatment of skin conditions, like hyperpigmentation, are summarized in the sections that follow.

Assays for Melanin Depigmentation

Reducing the pigment in melasma patients and preventing the production of melanin are two benefits of KA, according to substantial evidence. Numerous investigations into the impact of KA and KA esters' reduction of melanin have been carried out, and the results demonstrate the effectiveness of these agents.

A study conducted in vitro to assess KA's effectiveness in blocking melanogenesis on living pigment cells revealed promise. Moreover, the reduction of eumelanin content is influenced differently by hyperpigmented B16 cells and 5,6 DHI 2C, their vital precursor monomer.

According to a study (Lajis et al., 2012) looking into the depigmentation effect of KA esters (KA mono-oleate, KA mono-laurate, and KA mono-palmitate) on B16F1 melanoma cells, these esters effectively depigment melanoma cells at concentration ranges of (31.3 to 62.5) µg/mL.

At the lowest and maximum doses evaluated in this investigation (1.95 µg/mL), KA and KA esters demonstrated similar melanin inhibitory qualities. At doses ranging from 15.63 to 62.5 µg/mL, KA mono-palmitate demonstrated a marginally stronger inhibitory effect than the other derivatives.

Both the synthesized derivatives KA and hydroxycinnamic acid, when examined separately and in combination, were found by Lee et al. to have anti-melanogenic properties. The findings imply that KA's chelating component, rather than the hydroxycinnamic acid's phenol moiety, had a greater impact on tyrosinase inhibition. These investigations' anti-melanogenic activity also demonstrated that each of the substances under evaluation lowered tyrosinase activity in a way that was dose dependent [17].

SAFETY REGARDING HUMAN USE OF KOJIC ACID AND DERIVATIVES:

Studies on the safety and toxicity of kojic acid should be carried out, particularly for novel derivatives, given its wide range of uses and activities. Kojic acid has some negative side effects, including skin irritation and redness, which highlights the need for safety and toxicity research. Figure 2 provides a summary of the various factors considered both in vivo and in vitro when evaluating the safety of kojic acid and its derivatives.

The safety of treating melasma with kojic acid alone (1%), in combination with hydroquinone (2%), betamethasone (1%), or both agents at the aforementioned concentrations was also evaluated in the clinical trial intended to whiten the skin. A scale from 1 to 3 was used to rate the formulation's adverse effects, which included erythema, burning, and itching. Just three out of the 80 patients, who were split into four groups, reported having a burning sensation; these two patients were in the group that received kojic acid plus hydroquinone, and the other patient complained of kojic acid alone. It was proposed that the reason why the symptoms were relieved in both groups with betamethasone was because there were no reported side effects. When applied topically as a 1% concentration for the treatment of melasma, kojic acid was deemed safe. Kojic acid was administered intraperitoneally or orally to rats as part of in vivo studies. To confirm the hepatic carcinogenicity, initiation (DNA alterations), and promotion (gene activation) of kojic acid, F344 rats were given varying concentrations of the compound orally. Initiative effects and pre-neoplastic lesions were absent. In the context of promotion experiments, concentrations as low as 0.5 percent did not result in any changes. However, at 2% concentration, there was an increase in the area and quantity of placental form positive foci for glutathione S-transferase as well as in 8-OHdG levels, which are a sign of cellular oxidative stress during carcinogenesis. These findings showed that although kojic acid does not initiate hepatocarcinogenesis in rats, it does activate genes when present in high concentrations. To assess the toxicity on the liver or bone marrow, a repeated oral dose of kojic acid was tested in vivo in Crl: CD (SD) rats. There were no signs of micronuclei or changes to the DNA. Hepatocytes administered 1000 mg/kg/day for 14 days showed minimal hypertrophy. In the liver or bone marrow, repeated dosages of kojic acid did not cause genotoxicity. In addition to evaluating the safety of kojic acid derivatives administered intraperitoneally, an in vivo model was used to confirm their anticonvulsant activity. The incapacity of male mice to remain in a rod spinning at 6 rpm for one minute was used to measure neurotoxicity in these animals. In the tested concentrations (30, 100, and 300 mg/kg), the synthetic derivatives, 3-hydroxy-6-hydroxymethyl/methyl-2-substituted 4H-pyran-4-ones, were not toxic.

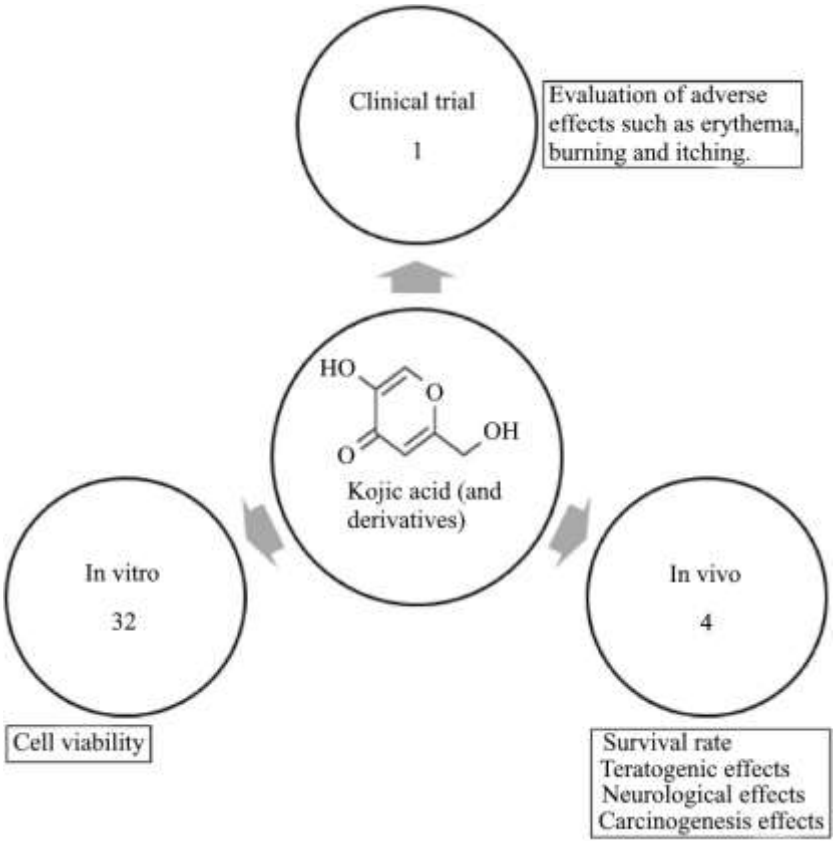

Figure 2. Overview of the main tests employed to evaluate kojic acid and its derivatives in the selected studies.

For the kojic acid ester-based nanoemulsion, an in vivo zebrafish model was used in the study. Underwent 96 hours of exposure to concentrations of the compound ranging from 7.81 to 500 μg/ml to determine its toxicity profile in zebrafish. As sample concentration increased, so did embryo mortality. Eighty percent of the embryonic zebrafish treated with 7.81–250 μg/ml survived. Survival embryos did not develop abnormally or deform. There was more than 500 μg/ml in the LC50, or 50% of the lethal concentration. As a result, the kojic acid ester-based nanoemulsion was found to be safe at the tested concentrations [18].

Studies focusing on the creation of formulations using nanotechnology for skin aging and hyperpigmentation employed in vitro MTT assays. Using J-774 mouse macrophages, Gonçalez and colleagues21 examined the cytotoxicity of liquid crystalline systems (nanotechnology-based drug delivery systems) containing 2% of kojic acid and contrasted them with kojic acid itself. Cellular viability exceeded 92%, and neither the formulations nor unencapsulated kojic acid showed signs of cytotoxicity. Similarly, Afifah and colleagues24 evaluated the cytotoxicity of an optimized kojic monooleate-enriched nanoemulsion using mouse embryonic fibroblast cells (3T3 cells) and found an IC50 value higher than 100 μg/ml. To evaluate the safety and cardiotoxicity of kojic acid, Chaudhari and colleagues also conducted in vitro tests using cell culture (human-induced pluripotent stem cell-derived cardiomyocytes, or hiPSC-CMs). Rather than utilizing the MTT assay, the extracellular LDH was assessed because its leakage can be a sign of membrane damage. Cell viability, beating rate, and genomic biomarkers were evaluated as well. At the tested concentrations of 1–400 μM, kojic acid did not change either cell viability or LDH leakage. At a 400 μM concentration, kojic acid enhanced the beating activity of hiPSC-CMs. For the cells treated with kojic acid, there were no changes in the genomic biomarkers' mRNA expression. 400 μM was the lowest observed effect concentration (LOEC) for kojic acid [19].

Cytotoxicity is typically assessed in both cancerous and normal cells, with the goal of achieving antitumor activity. It is important that the antitumor agent is safe for normal cells but toxic for cancerous cell lines. Cell lines that are not cancerous can be used, such as MRC-5 human lung cell lines and HGF-1 human gingival fibroblasts. Based on cell viability assays with IC50 determinations, the antitumor studies reviewed in this review showed that kojic acid derivatives had toxic effects on cancerous cell lines and safe concentrations for normal cell lines, suggesting that the studied kojic acid derivatives are safe molecules under these circumstances.

CONCLUSIONS

In summary, kojic acid and its derivatives have a wide range of applications in the fields of pharmaceutics, cosmetics, and medicine. In addition to being widely used and well-known for their ability to depigment skin, these molecules also can act as antioxidants, which enables them to be used as anti-aging agents. Additionally, kojic acid and its derivatives have been extensively described for their antibacterial, antifungal, and anti-inflammatory properties; their potential as antitumor substances may be taken into consideration due to the cytotoxicity results observed in cancerous cell lines, with both apoptotic and non-apoptotic pathways activated, without causing damage to normal cells. Other activities include anti-senescence of corneal cells, radioprotection, and anticonvulsant properties. KA and its derivatives' effectiveness has been assessed using a variety of techniques. The results of these investigations showed that these novel medications are useful in the treatment of melasma and hyperpigmentation, among other skin disorders. Furthermore, it was shown that KA derivatives inhibited tyrosinase more effectively than KA itself. Skin lightening agents, like KA, have demonstrated enhanced safety profiles when used for extended periods of time to treat skin conditions, like melasma, which can be managed with either monotherapy or combination therapy. More research on this topic will be supportive in producing safer and efficient agents for tyrosinase inhibition. When it comes to molecule stabilization and activity enhancement, using derivatives and nanocarriers has advantages. Based on published studies conducted in vitro and in vivo, kojic acid and its derivatives appear to be

safe substances that humans can use orally or topically. Additional studies on the subject are encouraged, particularly those pertaining to the safety and alternate uses of kojic acid and its derivatives.

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