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KOJIC ACID: A SKIN LIGHTENING AGENT

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ABSTRACT

This article deals with the study of kojic acid (KA), a tyrosinase inhibitor that has been extensively studied for its ability to lighten skin and treat hyperpigmentation, including melasma. KA, which is derived from fungi, reduces dark patches and UV-induced pigmentation by blocking the synthesis of melanin. To improve efficacy and stability, however, problems including cytotoxicity, instability, and skin irritation have led to a great deal of research on KA derivatives and combination therapy, especially with substances like hydroquinone and glycolic acid. The Cosmeceutical component Review (CIR) states that because of its cytotoxicity, this component (KA) can be used safely at concentrations up to 1%. Its safety at concentrations of 2% or less is further supported by other scientific studies. This study emphasizes the promise of KA for the long-term, efficient treatment of pigmentation problems in dermatology and cosmetics by highlighting its uses, safety profile, and developments in KA-based therapies.

KEYWORDS: Kojic acid, Tyrosinase inhibitor, Depigmenting agent, Hyperpigmentation, Melasma.

INTRODUCTION

Researchers worldwide are actively exploring the development of various tyrosinase inhibitors due to their significant impact on the cosmetic and pharmaceutical industries, as well as their broader economic implications. A key concern with these inhibitors is their safety, particularly when used frequently or in doses exceeding recommendations. High cytotoxicity and instability are among the challenges that need to be addressed, which has led to ongoing research to enhance their effectiveness and safety as cosmetic ingredients. Kojic acid (KA), a well-known tyrosinase inhibitor, has

been extensively studied within the cosmetic industry. KA and its derivatives are recognized for their radio protective, skin-lightening, anti-inflammatory, antioxidant, and anti-proliferative properties.[1] These characteristics enable KA to protect the skin from ultraviolet (UV) rays, reduce hyperpigmentation, and inhibit melanin production. KA is produced by various types of fungi and is also another consequence of the fermentation processes used in producing certain foods, such as soy sauce and sake.[2,3,4]

KA is widely incorporated into cosmetic products.[8] The Cosmetic Ingredient Review (CIR) panel has deemed KA safe for use in cosmeceuticals at concentrations of up to 1%. Furthermore, existing dermatological safety data supports the use of KA at concentrations of up to 2% in such products suggesting that this might be an appropriate upper limit.[5,6]

2. PRODUCTION [Methods]

In 1907, Saito found kojic acid (KA) in the mycelium of the fungus Aspergillus oryzae cultivated on steamed rice. As A. oryzae is frequently utilized in food industry too.[3,9,10] Initially, it was dubbed “Koji” after the fungus from which it originated.[7,11] Later, in 1913, Yabuta developed the term “kojic acid” and described its structure. Kojic acid, a fungus metabolite, is chemically identified as 5-hydroxy-2-hydroxymethylpyrone. In Japan, use as a food additive and is said to have health benefits. KA can be generated by many bacteria under varied aerobic circumstances utilizing distinct carbohydrate sources, and its lethal dose in live species is around 1g/kg. Aspergillus species fermentation in the atmosphere is thought to be a non-toxic and safe method of producing KA.[12]

Kojic acid is able to undergo a variety of chemical processes, including redox, acylation, alkylation, nucleophilic and electrophilic replacements, molecular ring opening, and chelation, because of its polyfunctional heterocyclic ring, which has an oxygen-containing backbone and many reactive sites. Different procedures that use mutant strains such as CCM-F-780 or CCM-F-781 to increase the production of KA have been devised for the fermentation process. Kojic acid is produced as a pale yellow, prismatic needle by a fermentation process that usually consists of multiple steps, the first of which is the inoculation of the medium with bacteria that produce kojic acid. Since 1955, there has been a kojic acid market. American enterprises and Pfizer were the pioneers in the production of this organic acid. These businesses have created processes for making kojic acid, recycling it, and creating derivatives that are applied as insecticides. The necessity of kojic acid has grown due to the growing interest in the cosmetics sector, and as a result, it is a major area of continuing study. The two primary areas of research that remain unabated despite the lengthy history of industrial production are strain creation and fermentation process optimization. The primary manufacturers of kojic acid are Aspergillus and Penicillium species, especially those from the flavus oryzae-tamarii group. It has been shown that certain species, including A. flavus, A. oryzae, A. tamarii, and A. parasiticus, are capable of producing significant amounts of kojic acid. Despite the fact that numerous strains with the ability to produce KA have been identified, little attention has been paid to modifying these strains by genetic engineering or mutation. Thus Tyrozinase inhibitors such as kojic acid are well known.[9,12,13]

2.1. Physical and chemical properties of KA

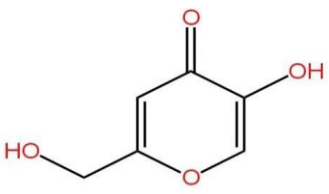

Fig. 1: Structure of Kojic acid.[14]

Kojic acid's chemical structure is identified as 5-hydroxy-2-hydroxymethyl-γ-pyrone. It is also known as 5- hydroxy-2-hydroxymethyl-4H-pyran-4-one and 5-hydroxy-2-hydroxymethyl-4-pyrone.[15] KA is a heterocyclic molecule with the structure illustrated in Figure 1. The crystals of KA are needle-like and colorless, subliming in a vacuum without any alterations. KA is soluble in specific organic solvents such as ethyl acetate, water, and ethanol, but it is unlikely to dissolve in ether, alcohol-ether mixtures, chloroform, or pyridine. The melting point of KA falls between 151–154°C.[9,16] According to Cryoscopy Technique, KA has a molecular weight of 142.1 and shows a maximum UV absorption peak at 260–284 nm.[3]

KA is a weak acid with diverse applications. It reacts at different positions on the ring, leading to the formation of various products such as ethers, pyridines, metal chelates, azo dyes, Mannich bases, and cyanoethylation products.[17,18] Several chemical reactions involving KA have been investigated over the years since its discovery, particularly at the carbon 5 position of this compound, the hydroxyl group functions as a weak acid, enabling it to form salts when it reacts with metals such as cadmium, nickel, copper, zinc, and sodium due to its slightly acidic nature. Adding new functional groups to the KA structure via the hydroxyl ketone or hydroxylalkyl groups can improve the solubility of the resulting complexes.[3]

Mode of action

The compound, In terms of chemical known as 5-hydroxy 2-hydroxy methyl 4-pyrone, inhibits tyrosinase by chelating copper ions (Cu^{+}) at the enzyme's active site. Tyrosinase is a key enzyme in melanin production, controlling the conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA). Skin depigmenting agents are generally categorized based on the stage of melanin synthesis they interfere with, and they may act before, during, or after melanin formation. Kojic acid (KA) functions as a skin lightening agent by acting directly during melanin synthesis. Historically, tyrosinase inhibitors have been among the most effective agents for skin lightening.[9,19]

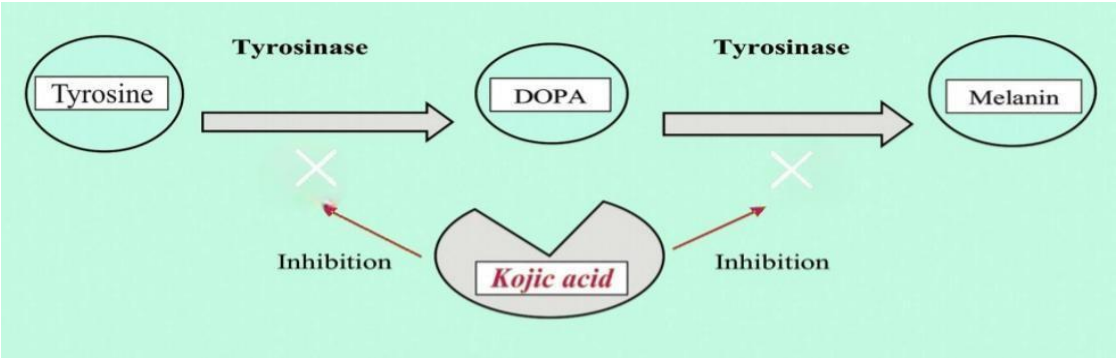

Fig. 2: MOA of KA.[5]

3. Guidelines for dosing and administration

Kojic acid (KA) is available over-the-counter (OTC) in gel or cream formulations with concentrations ranging from 1% to 4%. It is commonly combined with 2% hydroquinone in an α-hydroxy acid gel base. A recent randomized single-blind study used the melasma area severity index to assess the effectiveness of various treatments. The study compared 1% KA cream, 2% hydroquinone cream, and another treatment in patients with melasma. The combination of 1% KA cream with 2% hydroquinone cream demonstrated superior clinical effectiveness compared to other formulations

containing 1% KA cream.[9,20]

4. Kojic acid in food

The Aspergillus flavus group has conventionally been used to produce various foods such as miso (fermented soybean paste), soy sauce, and sake. Kojic acid (KA) is widely employed as a food additive used in the food sector to stop enzymatic browning in the food industry and to prevent unwanted darkening of agricultural products like vegetables, fruits, and crustaceans during storage. KA works by inhibiting polyphenol oxidase enzymes when these products are exposed to oxygen. Additionally, it is used in the production of raw noodles to prevent color changes and the formation of black spots by inhibiting tyrosinase activity.[9,21]

Derivatives of KA

KA is used less frequently in cosmetic goods because it irritates skin, has little inhibitory effect, and is unstable in storage.[4,40-43] There have been numerous KA derivatives created in an effort to address these drawbacks. Enhancing stability and solubility was the goal of creating these compounds. Tripeptide derivatives, hydroxyphenyl ether, amino acid derivatives, ester, and glycoside can all be produced by altering the alcoholic hydroxyl group of KA. The phosphonate is ethylene-linked with aldehyde to derivate KA, and the resulting intermediates have tyrosinase inhibitory activity that is approximately eight times that of KA itself. Techniques for the synthesis of several KA derivatives, including KA laureate, KA ester, and KA di-palmitate, have been published recently. Additionally, KA peptides have been studied as strong tyrosinase inhibitors.[3]

5. Treatment of hyperpigmentation

A condition known as skin hyperpigmentation occurs when certain areas of skin turn darker than the surrounding skin. This happens when particular areas of the skin produce too much melanin. The process known as melanogenesis produces melanin, a crucial pigment in skin hyperpigmentation. Melanosis is the term for an increase in the melanin pigment in epithelial cells. Dermal melanosis happens when melanin is present in the dermis between collagen bundles, while epidermal melanosis occurs when melanocytes are normal but melanin levels are elevated in hyperpigmented skin. Human skin, hair, and eyes are colored by the two types of melanin pigments that are produced by melanocyte cells (one melanocyte is surrounded by about 36 keratinocytes): eumelanin (black or brown) and pheomelanin (yellow reddish).There are three primary types of skin hyperpigmentation: age spot or liver spot, post-inflammatory hyperpigmentation, and melasma. Sun exposure, Addison's disease, hormonal imbalance, and vitamin B12 are the causes of skin hyperpigmentation.[22,23,24,25,26]

A variety of tyrosinase Inhibitory drugs have been used to treat pigmentation issues in recent years. These include kojic acid and its derivatives, arbutin, vitamin C, hydroquinone (HQ), glycolic acid (GA) and more. 5-Hydroxy- 2-hydroxymethyl-4H-pyran-4-one, often known as kojic acid (KA), is a noteworthy substance that is obtained from a variety of fungal species, such as Aspergillus, Penicillium, Alternaria, Pleospora, Sincephalstrom, Fusarium, and Mucor, among others. By utilizing its chelating qualities, preventing UV radiation, and binding to copper ions within the tyrosinase enzyme, KA counteracts free radicals and produces its skin-whitening action.[27] This multimodal strategy suppresses hyperpigmentation and prevents the tyrosinase enzyme from generating melanin.[24,28,29]

6. Treatment of melasma

Hyperpigmented brown to grayish brown macules on the face are a hallmark of melasma, an acquired pigmentary condition. Of all ethnic and racial groupings, it primarily affects women 90% of the time and 10% of men. Twenty to thirty

percent of women aged 40 to 65 in India had facial melasma. According on the lesion site and the depth of pigmentation, which can be ascertained histologically or instrumentally within the epidermis, dermis, or both, melasma is now classified. The precise etiology of melasma Is still unknown, however it is known that being exposed to UV light, elevated estrogen levels (mostly during pregnancy or the use of oral contraceptives), genetic susceptibility, and phototoxic medications all contribute significantly to the development of this hypermelanosis condition. Additional elements linked to its etiology include liver, thyroid, and/or ovarian disorders. UV radiation has been demonstrated to play a critical role in the development of melasma, namely in its aggravation.[29,30]

KA, has been used since the late 1980s as a skin-lightening agent because of its antioxidant and tyrosinase- inhibiting properties. Over-the-counter, it is a common component for melasma and hyperpigmentation.[31] Many fungus, including Aspergillus oryzae, Penicillium species, and Acetobacter species, are sources of kojic acid. Additionally, it attaches to the copper in tyrosinase, preventing eumelanogenesis and its action. Kojic acid, in combination with other lighteners, is used in 1%–4% concentrations to treat melasma. After 2-4 weeks of consistent use, its effects start to manifest, and they get better over the course of six months.[32,34,35]

7. Cosmetic application of KA

KA is a widely utilized chemical in many different sectors throughout the world.[39] It is applied topically to skin disorders such spots, melasma, and light brown patches brought on by post-inflammatory hyperpigmentation in the cosmetics industries.[44-47] Because KA inhibits the creation of tyrosinase, it inhibits the formation of melanin, which prevents the development of hyperpigmentation in human skin. It also possesses skin-lightening characteristics and can function as a UV protector. Because of its preservation qualities, KA also extends the shelf life of cosmetic goods. To treat age spots and lightened freckles, it is typically used with alpha-hydroxy acid in skin-lightening treatment formulations. Its manganese and zinc complexes allow it to be utilized as a γ-ray radioprotective agent.[3,35,36]

Table 1: Application of KA.[3]

APPLICATION OF KA -		
Tyrosinase Inhibitor	Production of Collagen	Lightens the skin
UV protector	Treatment for Melasma and Hyperpigmentation.	

8. Safety Assessment of KA

The safety and effectiveness of tyrosinase inhibitors in the pharmaceutical and cosmetics sectors have been assessed in a number of research. The fact that these inhibitors can stop pigmentation problems makes them significant. The safety studies conducted suggest that KA be used in topical treatments at a concentration of 1% or less because it exhibits effective and safe qualities within these levels. In Europe, KA is classified as a "additive" in the Inventory of Cosmetic Ingredients database, and its usage as a cosmetic ingredient is prohibited in nations like Switzerland. The safety of using 2% KA in leave-on cosmetics has been confirmed by additional skin sensitization evidence.[48] At 4%, KA depigmented the skin of black guinea pigs; however, at 1%, no such effects were seen. Additionally, the CIR Expert Panel recommended the use of 1% because they found that skin lightening and dermal sensitization would not occur at concentrations below that level. Additionally, KA was not hazardous in investigations on genotoxicity, reproduction, chronicity, or acuteness. Since KA is absorbed into the human skin gradually, it would not approach the limit of tumor promotion and low carcinogenicity, according to a different study on acute, chronic, reproductive, and genotoxic aspects conducted by Aytemir and Karakay (2012). Bearberry leaf-derived KA is safe and efficacious when applied topically, however it is not stable enough or effective enough to be used in cosmeceuticals.[49] It is safe to use at

concentrations between 0.1 and 2.0 percent, according to a survey done by the cosmetics industry. According to a ruling by the Scientific Committee on Consumer Products (SCCP) of the European Commission, KA is safe to use up to a 1% concentration limit. According to the information currently available, KA is safe to use as a skin-lightening agent in leave-on creams at a concentration of 1%. Numerous studies have demonstrated that KA does not exhibit any ocular or allergic sensitivities when taken at concentrations of 1% and 2%. Additionally, the International Agency for Research on Cancer (IARC) designated it as a group 3 carcinogen. Furthermore, the SCCP stated that the dosage of KA in skincare products should be 1.0% and that it is not a toxicant in its generative, chronic, acute, or genotoxicity forms, despite the FDA's prohibition on its use in pharmaceutical products without a prescription. Although KA has several advantages when used in topical solutions, there are also some drawbacks, such as contact dermatitis and potential skin photodamage.[3]

9. The effectiveness of KA as a skin lightening agent and its dangers

The primary therapeutic function of KA is to lighten obvious sun damage, age spots, or scars, which results in anti-aging effects on the skin. Additionally, the Cosmetic Ingredient Review Expert Panel (CIREP) has determined that a concentration of 1% is safe for use in cosmetics. In addition, KA has demonstrated antibacterial qualities that, even at low dilutions, can eliminate several common bacterial strains (such as acne-causing bacteria). Research has also indicated that KA may have antifungal properties. There have also been reports of treating ringworm, candidiasis, and yeast infections. When used cosmetically, KA is linked to several negative side effects and drawbacks. The primary adverse effect of KA is contact dermatitis, which is characterized by discomfort, itching, rashes, and irritated skin, particularly in sensitive skin types. When the concentration of KA is more than 1%, several adverse effects can be seen. Long-term usage of KA may result in further negative side effects, like sunburn on delicate skin. On damaged skin, KA may possibly cause skin cancer. However, more research is required to determine any additional possible advantages or disadvantages of KA.[5]

10. Combination of KA and their effectiveness

When it comes to treating face melasma, 4% hydroquinone and 0.75% kojic acid + 2.5% vitamin C are excellent topical hypopigmenting treatments.[26] Conversely, 4% hydroquinone is a superior topical hypopigmenting treatment with a faster rate of clinical improvement than cream containing 0.75% kojic acid.[37,38] The combination of Glycolic Acid and KA has demonstrated good therapeutic efficacy, according to Cotellessa et al. Glycolic acid with 5% KA was more effective (28%) than glycolic acid with 5% HQ (21%).[38]

11. Comparative study of safety and efficacy on KA and it's combination

Patients were randomly assigned to four parallel groups of 20 patients each using simple randomization. Each of the groups received a topical application once a night (group A received 1% cream of kojic acid, group B received 1% cream of kojic acid and 2% cream of hydroquinone, group C received 1% cream of kojic acid and betamethasone valerate 0.1%, and group D received 1% cream of kojic acid, 2% hydroquinone, and betamethasone valerate 0.1% cream). Additionally, each group received a sunscreen with an SPF15 for use during the day. Utilizing bivariate analysis that is, computing the average and standard deviation the effectiveness was assessed by determining the percentage decrease in MASI scores between the groups at the conclusion of three months. In order to assess safety, adverse symptoms like burning, erythema, and itching were noted using a 0–3 rating system, where 0 denotes no impact, 1 mild, 2 moderate, and 3 severe. According to a research by Fulton et al., 20 (51%), out of 39 individuals who received 4% hydroquinone

or 2% kojic acid on either cheek, responded equally to both treatments. In the Lim et al. trial, 60% of cases that used a 2% hydroquinone and 2% kojic acid gel responded better than those that applied hydroquinone alone, which only produced responses in 47.5% of instances.[20] The group that improved the least (36.46%) was group C, which included 1% kojic acid and 0.1% betamethasone valerate cream. The effectiveness of kojic acid in conjunction with a topical corticosteroid has not been reported in any literature. The mean percentage change in MASI score for group D (1% kojic acid, 2% hydroquinone, and 0.1% betamethasone valerate in a cream base) was 54.03%, with 25% are demonstrating great progress, 35% are responding well, 35% are responding well, and 5% are responding poorly. In terms of efficacy, this group came in third. As a result, kojic acid and hydroquinone work better together as a depigmenting agent than the other three combinations in this study. It works well when combined with hydroquinone.[50,51]

RESULT

As per studies, when KA is used in combination with hydroquinone and other skin-lightening agents, its efficacy appears to increase, suggesting a synergistic effect that could be beneficial for treatment formulations. Thus, additional clinical research is required in order to design and develop new KA-based therapies.

CONCLUSION

According to study, Research on kojic acid (KA) and its derivatives has shown that they are effective tyrosinase inhibitors, making them valuable for skin-lightening applications. Studies have demonstrated that KA derivatives inhibit tyrosinase more effectively than KA itself, offering potential improvements in both efficacy and safety.In terms of safety, kojic acid and its derivatives are safe substance for human use at the measured quantities.

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