

Use of Kojic Acid in Cosmetics

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In 1907, Saito discovered Kojic Acid (KA), a natural product; it has since become one of the most investigated skin-lightening agents. KA inhibits tyrosinase and has been commonly researched in the cosmetic industry. It is incorporated in many kinds of cosmetic products.

Keywords: Kojic acid ; hyper-pigmentation ; tyrosinase ; melasma ; cytotoxicity ; sensitization

1. Introduction

Global researchers are exploring the development of various groups of tyrosinase inhibitors, as they have a huge impact on the cosmetic and pharmaceutical industries and the global economy ^[1]. One of the main considerations for tyrosinase inhibitors is safety, particularly when applied regularly and not considering the recommended dosages. Some challenges experienced with the use of these agents include high cytotoxicity and instability, thus necessitating additional research to improve their applications as ingredients in cosmetics ^{[1][2]}.

KA inhibits tyrosinase and has been commonly researched in the cosmetic industry ^{[1][2][3][4][5][6]}. KA and its derivatives have radioprotective, skin-lightening, anti-inflammatory, anti-oxidant, and anti-proliferative properties ^{[1][7]}. Due to its tyrosinase inhibitory activity, KA can protect the skin from ultraviolet (UV) rays, reduce hyperpigmentation, and prevent melanin formation ^{[1][8]}. It is produced by several types of fungi, and it is also a by-product of the fermentation process of certain foods, such as soy sauce and sake ^[1].

KA is incorporated in many kinds of cosmetic products ^[9]. The CIR approved KA as safe at a concentration of 1% in cosmeceutical products ^[9]. The existing dermatological safety data also support the safety of KA at a concentration of 2% in cosmeceuticals, indicating that a limit of 2% might be applicable ^[9].

2. Physical and Chemical Properties of Kojic Acid

KA chemical structure is defined as 5-hydroxy-2-hydroxymethyl-γ-pyrone ^[10]. It is also known as 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one and 5-hydroxy-2-hydroxymethyl-4-pyrone ^{[10][11]}.

The crystals of KA are acicular and colorless, and they sublime in a vacuum with no variations. KA is soluble in some organic solvents, such as ethyl acetate, water, and ethanol. It is unlikely to dissolve in ether, alcohol ether mixture, chloroform, and pyridine ^{[10][12]}.

The melting point of KA lies between 151–154 degrees Celsius (°C) ^{[10][12]}. According to Cryoscopy Technique, the molecular weight of KA is 142.1, and its maximum peak of UV Absorption Spectra is at 260–284 nanometers (nm).

KA is a weak acid with multidimensional uses. It reacts at every position on the ring, thus forming several products, such as ethers, pyridines, metal chelates, azodyes, mannich base, pyridines, and cyanoethylation products ^{[10][12]}. Several chemical reactions of KA have been studied over the years since its isolation. At the carbon 5 position of this compound, the hydroxy becomes a weak acid, therefore forming salts when reacted with metals such as cadmium, nickel, copper, zinc, and sodium due to its weakly acidic properties ^[10]. Introducing new functional groups on the KA skeleton via the hydroxy ketone or hydroxyalkyl allows for the improvement in the solubility of subsequent complexes ^[13].

3. Safety Assessment of Kojic Acid

Several studies have been conducted to evaluate the safety and efficiency of tyrosinase inhibitors in the cosmeceutical and medicinal industries ^{[2][14]}. These inhibitors are important due to their ability to prevent pigmentation disorders.

The safety studies performed recommend the use of KA in topical preparations at a concentration of 1% or less because, in these ranges, it shows efficient and safe properties [2].

KA is listed as an 'additive' in the Inventory of Cosmetic Ingredients database of Europe, and in countries such as Switzerland, there is a ban on the use of KA as a cosmetic ingredient [15]. Other skin sensitization data have reinforced the safety of KA at a dosage of 2% in leave-on products [1][14][16]

KA depigmented black guinea pig skin at a dosage of 4%, but these results were not observed at 1%. The CIR Expert Panel also concluded that at concentrations below 1%, dermal sensitization and skin lightening would not be seen, thus recommending the usage at 1% [9][17].

KA was also not found to be toxic in chronic, reproductive, genotoxicity, and acute studies [14] Another study on acute, chronic, reproductive, and genotoxic aspects by Aytemir and Karakay (2012), revealed that KA was not toxic, as it is slowly released into the human skin; it would not reach the limit of tumor promotion and low carcinogenicity [1].

KA produced from bearberry leaves is safe and efficient for topical use, although it is not satisfactorily effective and not stable for use in cosmeceuticals [1][7][18].

A survey conducted by the cosmetics industry also indicated that it is safe for use at a concentration ranging from (0.1 to 2.0)% [14][16]

A determination by the European Commission's Scientific Committee on Consumer Products (SCCP) indicated that KA is safe for use at a concentration limit of 1% (Burnett et al., 2010; Mann et al., 2018).

Available data to date indicate that KA is safe for application as a skin lightening agent at a concentration of 1% in leave-on creams [2][9].

Various investigations have shown that when used at 1 and 2%, KA does not show any ocular or allergenic sensitivity. It was also declared a group 3 carcinogen by the International Agency For Research On Cancer (IARC) [2]. In addition, the Food and Drug Administration (FDA) does not permit the use of KA in pharmaceutical products without a prescription; however, the SCCP reported that the dose of KA should be 1.0% in skincare products and that it is not a toxicant in generative, chronic, acute, and genotoxicity form [2].

Despite the extensive benefits of using KA in topical products, there are some disadvantages, including contact dermatitis and possible photo-damaging of the skin [2]. These are outlined in **Table 1** below.

Table 1. Positive and negative effects of using KA for skin lightening.

Benefits	Disadvantages
- Lightening effect on visible sun damage and age spots - Anti-aging - Antimicrobial - Antifungal - Anti-acne - Treatment of yeast infections, candidiasis, and ringworm	- Contact eczema (especially in sensitive skins) - Long-term use of KA may make skin more prone to sunburn - Carcinogenic when used on damaged or broken skin

4. Kojic Acid Derivatives

KA causes skin irritation, has inadequate inhibitory activity, and is not stable during storage, thus reducing its use in cosmetic products [1][15][19][20][21]. To overcome these disadvantages, many derivatives of KA have been produced [22]. These derivatives were produced to improve stability and solubility.

By modifying the alcoholic hydroxyl group of KA, it can be converted into an ester, glycoside, amino acid derivatives, hydroxyphenyl ether, or tripeptide derivatives [1].

The KA derivatized through an ethylene linkage of the phosphonate with aldehyde using intermediates derived from KA is about eight times more effective in tyrosinase inhibitory activity than KA [1][10].

Recently, methods for the synthesis of a variety of KA derivatives, such as KA di-palmitate, KA ester, and KA laureate, have been reported [10][23]. KA peptides have also been investigated as potent tyrosinase inhibitors [24].

5. Cosmetic Applications of Kojic Acid

KA is a popular ingredient and is used by various industries globally [25][26]. In the cosmetic industry, it is used as a topical treatment for skin conditions such as spots, melasma, and patches of light brown color resulting from post-inflammatory hyperpigmentation [25][27][28][29][30].

KA has skin-lightening properties and can act as a UV protector, whereby it prevents the development of hyperpigmentation in human skin by inhibiting the formation of melanin through the prevention of tyrosinase formation [10][26][28].

KA also enhances the shelf life of cosmetic products through its preservative properties [31]. It is normally combined with alpha-hydroxy acid in the formulation of skin-lightening products to manage age spots and lightened freckles. Due to its manganese and zinc complexes, it can be used as a radioprotective agent against γ -ray [10]. **Figure 1** below summarizes the above-discussed applications of KA.

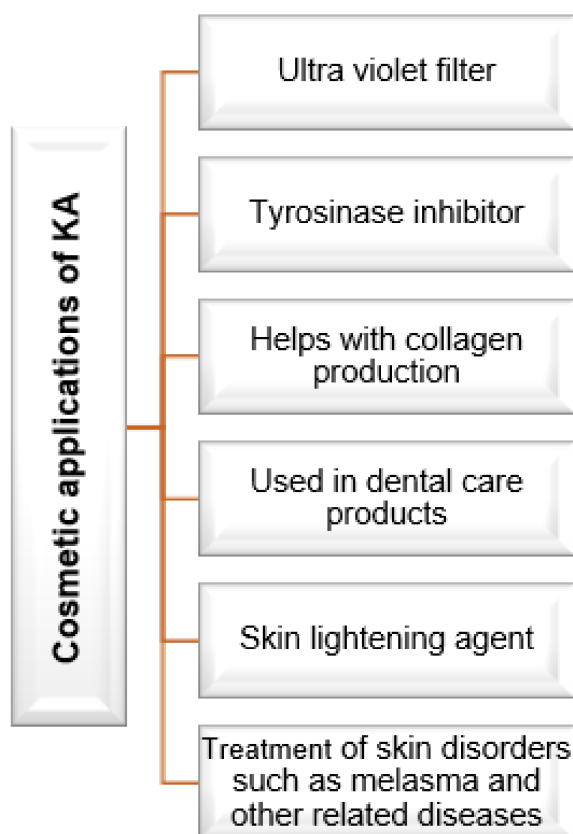


Figure 1. Cosmetic applications of kojic acid [2].

6. Biological Activities of Kojic Acid

The available literature indicates that this ingredient has various biological activities, and they are listed below.

6.1. Antibacterial and Antimicrobial Activity

KA has antifungal and antibacterial properties [32]. Preceding antimicrobial activity assays showed that KA was more active against Gram-negative bacteria than against Gram-positive bacteria [1]. However, some of its derivatives have shown conflicting effects distinct from KA's antibacterial activity [1].

When used in cosmetic products, KA can prevent the growth of microorganisms and can be used as a preservative [33].

The antimicrobial activity of the ethyl acetate (EtOAc) extract of *Colletotrichum gloeosporioides* and its major compound KA were evaluated, and the results showed considerable antimicrobial activity against all tested strains [29]. When tested against various microorganisms, KA was most active against *Micrococcus luteus* and least active against *Pseudomonas aeruginosa* [29].

Due to its antifungal properties, KA is incorporated into some antifungal products to improve their effectiveness [29]. Furthermore, it could be useful in treating various fungal infections of the skin as well as yeast infections, ringworm, athlete's foot, and candidiasis [29].

KA and its derivatives have potent activity against bacteria such as *Staphylococcus aureus* [10]. The KA derivatives were also validated for antifungal activities against *Fusarium oxysporum*, *Rhizoctonia solani*, and *Pythium graminicola*, which cause fungal infections such as *fusarium* wilt, sheath blight, and seedling blight. Besides its antibiotic properties, KA also shows some insecticidal activity against *Spodoptera frugiperda* and *Heliothis zea* insects [10].

6.2. Antioxidant Activity

KA has anti-oxidant properties [7] and is used as a substitute for hydroquinone (HQ) for skin lightening by the cosmeceutical industry [1][34].

Studies by Zhang et al., (2017) showed that KA improved oxidative stress response in fungi, thus showing the anti-oxidant ability of this metabolite [34]. Other preceding bioactivity studies on KA revealed that it has anti-oxidant properties [29].

The correlation between anti-melanogenic activity with oxidative effects of KA and KA esters was investigated by Lajis et al., 2012. The results of the study showed that both KA and its esters had mild free radical scavenging activities at concentrations ranging from 1.95 to 1000 µg/mL [35].

6.3. Anti-Inflammatory Activity

KA may exert slight anti-inflammatory effects that may favorably improve by subsequent derivation of chosen KA derivatives [36]. In a recent study to develop a safe anti-inflammatory compound, a derivative of KA and p-coumaric acid were synthesized, as they are known to have anti-inflammatory properties. The study suggested that the anti-inflammatory action of KA was enhanced by the addition of cinnamate moiety in p-coumaric acid as an hydrophobic part [37]. A study assessed the anti-inflammatory activity of KA and p-coumaric acid and revealed that both possessed anti-inflammatory properties [34].

In another study, KA and its two novel derivatives were isolated from the fungus *Aspergillus versicolor* and evaluated for their anti-inflammatory effects [38], showing that KA has a moderate anti-inflammatory effect, while the derivatives 1 and 2 were found to have improved effects [38].

6.4. Tyrosinase Inhibition Activity

KA is regarded as one of the best skin-lightening agents in the beauty industry [1]. It exerts a slow and effective reversible inhibition of tyrosinase, thus preventing melanin formation, and also plays an important role in cellular melanin formation [1]. According to available data from various studies, it can be used as a monotherapy or combined with other agents [27]. In Japan, this ingredient is known as a quasi-drug [14][39]. Due to its ability to inhibit tyrosinase activity, KA has been used in several studies as a standard [1][24][40][41][42][43][44][45]. Another study revealed that KA inhibits melanosis by interfering with the uptake of oxygen required for enzymatic browning [1].

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