Review on the Use of Kojic Acid—A Skin-Lightening Ingredient

Vivey Phasha 1, Jeremiah Senabe 1, Phatheka Ndzotoyi 1, Blessed Okole 1, Gerda Fouche 2 and Anil Chuturgoon 3,*

1 Council for Scientific and Industrial Research, Pretoria 0001, South Africa; vphasha@csir.co.za (V.P.); jsenabe@csir.co.za (J.S.); bokole@csir.co.za (B.O.); pndzotoyi@csir.co.za (P.N.)
2 Department of Chemistry, Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria 0028, South Africa; fouche51@gmail.com
3 School of Laboratory Medicine and Medical Sciences, Durban 4319, South Africa
* Correspondence: CHUTUR@ukzn.ac.za

Abstract: This article reviews the use of Kojic Acid (KA) as a skin-lightening ingredient in the cosmetics industry. In 1907, Saito discovered KA, a natural product; it has since become one of the most investigated skin-lightening agents. This paper highlights the findings of the research conducted on this agent. It has been found that KA has certain disadvantages, and researchers have attempted to mitigate these disadvantages by designing new equivalents of KA that are more efficient in tyrosinase inhibition. These equivalents are also safe to use and have improved properties and solubility. The Cosmeceutical Ingredient Review (CIR) indicates that this ingredient can be safely used at a concentration not higher than 1% due to its cytotoxicity. Other scientific data also support its safety at a concentration of 2% or less. It was shown to be helpful in the treatment of hyper pigmentary disorders, such as freckles, age spots, post-inflammatory hyperpigmentation, and melasma, which has been proven clinically.

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 [1–6]. 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. Fungi-Producing Kojic Acid

KA was discovered in 1907 by Saito in cultures of Aspergillus oryzae [10,11]. This organic acid is formed when various types of fungi ferment. KA is mostly secreted by more than 58 fungal strains of the Aspergillus genus [10]. Some of the species that form...
this acid include *Aspergillus*, *Penicillium*, *Acetobacter*, and others [2,10,12–14]. Amongst the *Aspergillus* species, its main producers are *Aspergillus oryzae*, *Aspergillus flavus*, and *Aspergillus parasiticus* (Table 1) [15–18]. It is used in the food and cosmeceutical industries for preserving or changing the color of substances. In the cosmetic industry, it is well known for its tyrosinase inhibition activity [19,20].

Table 1. Production of KA. Adapted from Chaudhary, 2014 [10].

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Toxins</th>
<th>Characteristics</th>
<th>Production Yield</th>
</tr>
</thead>
</table>
| *Aspergillus flavus* | Aflatoxins, Aflatrem, Aspergilic acid, Cydopazonic acid, β-nitropionic acid, and Serigmatocyctin | **Pathogenicity**: Generally, a contaminant but also known to cause disease; commonly associated with aflatoxins  
**Macroscopic morphology**: Velvety, yellow to green or brown, Reverse goldish to red-brown  
**Macroscopic morphology of conidiophores**: Variable length, rough, pitted, spiny  
**Macroscopic morphology of conidiophores**: Uni-seriate and bi-seriate, covers entire vesicle, points out in all directions | High              |
| *Aspergillus oryzae* | Aspergillus acid, Cycopiazonic acid, Maltoryzine β-nitropropionic acid, Ochtratoxins |                                                                                  | Medium to High   |
| *Aspergillus parasiticus* | Aflatoxins, Aspergillic acid, and Sterigmatocyctin |                                                                                  | High             |
| *Aspergillus Tamarii* | Aflatoxins                           |                                                                                  | Low              |

3. Physical and Chemical Properties

KA chemical structure is defined as 5-hydroxy-2-hydroxymethyl-γ-pyrone [14]. It is also known as 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one and 5-hydroxy-2-hydroxymethyl-4-pyrene [14,21]. KA is a heterocyclic compound with a structure as shown in Figure 1 below.

![Figure 1. Kojic acid chemical structure, Adapted with permission from Ref. [6], 2020, Hasil et al.](image)

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 [10,14].

The melting point of KA lies between 151–154 degrees Celsius (°C) [10,14]. 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 [10,14]. 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 [14]. Introducing new functional groups on the KA skeleton via the hydroxy ketone or hydroxyalkyl allows for the improvement in the solubility of subsequent complexes [22].

4. 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 [2,23]. 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 [13]. Other skin sensitization data have reinforced the safety of KA at a dosage of 2% in leave-on products [1,23,24].

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% [9,25].

KA was also not found to be toxic in chronic, reproductive, genotoxicity, and acute studies [23]. 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)% [23,24].

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 2 below.

Table 2. Positive and negative effects of using KA for skin lightening.

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

5. Kojic Acid Derivatives

KA causes skin irritation, has inadequate inhibitory activity, and is not stable during storage, thus reducing its use in cosmetic products [1,13,26–28]. To overcome these dis-
advantages, many derivatives of KA have been produced [29]. 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 [1,14].

Recently, methods for the synthesis of a variety of KA derivatives, such as KA di-palmitate, KA ester, and KA laureate, have been reported [14,30]. KA peptides have also been investigated as potent tyrosinase inhibitors [31].

6. Cosmetic Applications of Kojic Acid

KA is a popular ingredient and is used by various industries globally [15,19]. 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 [15,32–35].

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 [14,19,33].

KA also enhances the shelf life of cosmetic products through its preservative properties [36]. 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 $\gamma$-ray [14]. Figure 2 below summarizes the above-discussed applications of KA.

![Figure 2. Cosmetic applications of kojic acid [2].](image)

7. Biological Activities of Kojic Acid

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

KA has antifungal and antibacterial properties [37]. 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 [38].

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 [34]. When tested against various microorganisms, KA was most active against *Microoccus luteus* and least active against *Pseudomonas aeruginosa* [34].

Due to its antifungal properties, KA is incorporated into some antifungal products to improve their effectiveness [34]. Furthermore, it could be useful in treating various fungal infections of the skin as well as yeast infections, ringworm, athlete’s foot, and candidiasis [34].

KA and its derivatives have potent activity against bacteria such as *Staphylococcus aureus* [14]. 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 [14].

7.2. Antioxidant Activity

KA has anti-oxidant properties [7] and is used as a substitute for hydroquinone (HQ) for skin lightening by the cosmeceutical industry [1,39].

Studies by Zhang et al., 2017 showed that KA improved oxidative stress response in fungi, thus showing the anti-oxidant ability of this metabolite [39]. Other preceding bioactivity studies on KA revealed that it has anti-oxidant properties [34].

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 [40].

7.3. Anti-Inflammatory Activity

KA may exert slight anti-inflammatory effects that may favorably improve by subsequent derivation of chosen KA derivatives [41]. 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 [42]. A study assessed the anti-inflammatory activity of KA and p-coumaric acid and revealed that both possessed anti-inflammatory properties [39].

In another study, KA and its two novel derivatives were isolated from the fungus *Aspergillus versicolor* and evaluated for their anti-inflammatory effects [43], showing that KA has a moderate anti-inflammatory effect, while the derivatives 1 and 2 were found to have improved effects [43].

7.4. 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 [32]. In Japan, this ingredient is known as a quasi-drug [23,44]. Due to its ability to inhibit tyrosinase activity, KA has been used in several studies as a standard [1,31,45–50].
Another study revealed that KA inhibits melanosis by interfering with the uptake of oxygen required for enzymatic browning [1].

8. Kojic Acid Mechanism of Action

KA is a kind of secondary metabolite, whose biosynthesis pathway continues to be uncertain to date [11]. However, it is stated that it chelates divalent ions and acts as a tyrosinase inhibitor and a free radical scavenger [19,51]. It works by chelating the copper (Cu²⁺) at the active site of the tyrosinase enzyme [8,52]. The tyrosinase enzyme, also known as polyphenol oxidase, limits the rate of melanin synthesis, and it is responsible for converting L-tyrosine to L-3–4 dihydroxyphenylalanine [8,19,27]. It belongs to the type 3 copper-containing protein family, with two copper ions (CuA and CuB) in the active site [53]. CuA and CuB catalyze the conversion of monophenols (e.g., tyrosine) into o-diphenols (monophenolase activity) followed by the oxidation of the o-diphenols to the resultant o-quinone derivatives (diphenolase activity) (Figure 3) [54].

Figure 3. The reaction catalyzed by tyrosinase. Adapted with permission from Ref. [55], 2018, Lai et al.

Low-pigmenting agents can be generally classified according to which step of melanin production is disrupted [55]. This depends on whether the agents can act before, during, or after melanin production. KA acts during the actual synthesis of melanin, exhibiting a sufficient inhibitory effect on monophenolase activity and a varied inhibitory effect on the diphenolase activity of mushroom tyrosinase [55].

8.1. Assays for Evaluating the Efficacy of Kojic Acid

The efficacy of KA may be assessed by several methodologies, varying from in vitro experiments to in vivo and clinical studies. All these methods have their advantages and disadvantages and may, from time to time, lead to false positives and false negatives [56]. The following sections describe some of the findings from previous studies conducted on the efficacy of KA in treating or managing skin disorders such as hyperpigmentation.

8.2. Melanin Depigmentation Assays

There is substantial evidence indicating that KA is effective in inhibiting melanin production and reducing the pigment in melasma patients [57]. To investigate the effect of melanin reduction by KA and KA esters, various studies have been conducted, and they reveal the efficacy of these agents.

An in vitro study to evaluate the capacity of KA to inhibit melanogenesis on living pigment cells showed that it is effective. In addition, hyper-pigmented B16 cells, and their essential precursor monomer, 5,6 DHII2C, influence a different eumelanin content reduction [14].

A study to investigate the depigmentation effect of KA esters (KA mono-oleate, KA mono-laurate, and KA mono-palmitate) on B16F1 melanoma cells was conducted (Lajis et al., 2012), which revealed that these esters at a concentration range of (31.3 to 62.5) µg/mL efficiently depigment melanoma cells [40].

KA and KA esters showed comparable melanin inhibitory properties at the minimum and maximum doses assessed in this study (1.95 µg/mL). However, KA mono-palmitate showed a somewhat greater inhibitory effect than the other derivatives assessed at doses of (15.63 to 62.5) µg/mL [40].
Lee et al. evaluated the anti-melanogenic effects of the synthesized derivatives KA and hydroxycinnamic acid individually and in combination and found that both had anti-melanogenic properties [58]. The results suggest that the chelating portion of KA had more effect on tyrosinase inhibition than the phenol moiety of hydroxycinnamic acid [58]. The anti-melanogenic activity from these studies also showed that all the compounds evaluated reduced tyrosinase activity in a dose-dependent manner [58].

8.3. Tyrosinase Inhibition Assays

Tyrosinase inhibition is the safest and most effective approach to minimizing hyperpigmentation [59]. However, there is a limitation in the clinical efficacy of the currently used tyrosinase inhibitors, as these inhibitors were specifically chosen based on their ability to inhibit mushroom tyrosinase [59]. This is also a widely reported screening method in the literature for skin-lightening ingredients [60]. Tyrosinase is an enzyme responsible for synthesizing melanin through melanogenesis [61].

Lajis et al. (2012) further investigated the inhibitory effect of KA and its esters at safe dosages of (1.95 to 62.5) µg/mL [40]. When pigmented melanoma B16F1 cells were incubated with KA and its derivatives, a major reduction in tyrosinase activity was revealed at (31.25 to 62.5) µg/mL [40].

At minimal doses of (1.95 to 15.25) µg/mL, KA and its derivatives showed a minor reduction in tyrosinase activity [40].

The available IC$_{50}$ values for KA tyrosinase inhibitory effect ranges from (6 to more than 100) mmol/L [24]. An in vivo study to compare KA with several phenolic-derived compounds on the catalysis of human tyrosinase and synthesis of melanin was conducted [24]. It was revealed that KA is less effective in tyrosinase inhibition, with an IC$_{50}$ of about 0.5 mmol/mL [24]. KA also shows a non-competitive inhibition, with an inhibitory constant value of 0.145 mmol/mL, indicating selective binding to the deoxy form [24].

Amongst the KA esters, KA monooleate inhibited mushroom tyrosinase more than KA monolaurate and KA mono-palmitate. The KA monooleate inhibitory effect on mushroom tyrosinase was more or less similar to that of KA at doses of (62.5 to 250) µg/mL [40].

Another study to assess the tyrosinase inhibition of KA derivatives was conducted by Rho et al., (2010), where a series of KA derivatives comprising sulfoxide, sulfone, and thioether bonds were produced. In the tyrosinase assay, KA thioether derivatives comprising suitable lipophilic alkyl chains exhibited effective inhibitory activity [62].

8.4. Mushroom Tyrosinase

Mushroom tyrosinase is the most commonly used method to screen for tyrosinase inhibitors [61]. In most of these studies, the tyrosinase activity is expressed as the half-maximal inhibitory concentration (IC$_{50}$), which is the concentration of the samples producing 50% inhibition [5].

KA demonstrates a great inhibitory outcome on monophenolase activity and a non-competitive inhibitory outcome on the diphenolase activity of mushroom tyrosinase [1,19,55].

In a study by Aytemir et al., KA (10 µM) showed the best inhibitory properties against mushroom tyrosinase activity, cellular tyrosinase activity, and cellular melanin formation [1].

Khezri et al., 2021, evaluated the tyrosinase inhibitory activity of a KA derivative (KA-nano structured lipid carrier (NLC$_{3}$)) against mushroom tyrosinase. The results obtained revealed that the prepared NLC$_{3}$ and KA solutions inhibited the activity of tyrosinase mushroom in a concentration-dependent manner; however, KA-NLC$_{3}$ showed greater potency in tyrosinase inhibitory activity than pure KA [51]. KA was previously found to be attached at the entrance to the active site of Bacillus megaterium tyrosinase, recommending one considerable intermediate binding site. However, the full mechanism of KA inhibition continues to be unclear [53].

An et al., 2010, conducted a study to compare the inhibitory effects of p coumaric acid (pCA), arbutin, and KA on the catalytic activities of mushroom, murine, and human
tyrosinases in vitro, using tyrosine and 3,4 dihydroxyphenylalanine as substrates. The results revealed that pCA is a greater inhibitor of human or murine than mushroom tyrosinase, in comparison with KA and arbutin as a positive control. Furthermore, pCA showed inhibition of human tyrosinase at much lower concentrations than those required for the inhibition of murine or mushroom tyrosinase [5].

8.5. In Vivo Clinical Studies

Studies have shown that hyperpigmentation, particularly melasma, greatly affects quality of life, causing psychosocial distress. Treatments for melasma include topical depigmenting agents such as KA [3]. The efficacy of a given ingredient may be evaluated by clinical trials. Depigmentation of the affected skin areas may be evaluated visually, which may be done using color charts such as Munsell or by measuring with cutaneous colorimeters [56,63]. The results in both cases depend on the nature and size of the studied skin area; furthermore, after the observation, it can only be recommended that both methods are concurrently used [56].

In a clinical trial, a formulation containing 1.0% KA was shown to be effective in the treatment of hyper pigmentary conditions, such as freckles, age spots, post-inflammatory hyperpigmentation, and melasma [44].

Another study to determine the effects of adding KA to a formulation comprising two other lightening agents in 40 females with epidermal melasma was conducted. It was stated that more than half of the melasma was cleared in 60% of the patients treated with KA compared to 47.5% of patients treated with a formulation without KA [32].

A 12-week trial to test the efficacy of KA as a skin lightener in patients with dyschromia revealed that patients treated with Vitamin C/KA had greater improvement in the appearance of dyschromia, skin tone, and radiance when compared to patients treated with HQ. In this study, KA was better tolerated with less stinging and tightness to the skin [35].

KA has been combined with other therapies to treat facial hyperpigmentation. In a randomized, split-face study of 39 patients with facial hyperpigmentation, it was revealed that 51% of patients had an equal decrease of melasma on both the KA 2% plus glycolic acid (GA) 5% side and the HQ 2% plus GA 5% sides of their faces [64]. Additionally, 28% and 21% of patients saw benefits with KA and HQ, respectively, indicating that KA and 2% HQ are equally effective in the treatment and management of melasma [64].

The efficacy of KA and other agents in treating melasma was evaluated by Desai et al., 2019, in a randomized clinical study of 55 healthy subjects [3]. A hydro glycolic topical face serum containing tranexamic acid, KA, niacinamide, and hydroxyethylpiperazineethane sulfonic acid was used as a treatment [3]. Significant reduction in hyperpigmentation increased skin texture, and skin tone homogeneity was observed in the patients. A major reduction in melasma was also observed at all time points afterwards [3]. Table 3 shows a summary of the above-mentioned clinical trials conducted on KA.

<table>
<thead>
<tr>
<th>Study Design and Setting</th>
<th>Concentration</th>
<th>Dosing Regimen (Weeks)</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of freckles, age spots, post-inflammatory hyperpigmentation, and melasma</td>
<td>1%</td>
<td>-</td>
<td>Effective</td>
<td>[44]</td>
</tr>
<tr>
<td>KA was combined with two other lightening agents in 40 females to treat epidermal melasma. Treatment on half of the face with KA. The other half was treated with the same application with no KA.</td>
<td>5%</td>
<td>-</td>
<td>Effective</td>
<td>[32]</td>
</tr>
</tbody>
</table>
Table 3. Cont.

<table>
<thead>
<tr>
<th>Study Design and Setting</th>
<th>Concentration</th>
<th>Dosing Regimen (Weeks)</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin lightening in patients with dyschromia</td>
<td>Not stated</td>
<td>12</td>
<td>Effective</td>
<td>[35]</td>
</tr>
<tr>
<td>KA was combined with other therapies to treat facial hyperpigmentation and melasma in 39 patients</td>
<td>KA 2% plus glycolic acid (GA) 5% side and HQ 2% plus GA 5%</td>
<td>Effective</td>
<td>[64]</td>
<td></td>
</tr>
<tr>
<td>The efficacy of KA and other agents in treating melasma in a randomized clinical study of 55 healthy subjects</td>
<td>1% KA, 5% niacinamide, and 3% Traxenamic acid</td>
<td>Significant reduction</td>
<td>[3]</td>
<td></td>
</tr>
</tbody>
</table>

9. Conclusions

Kojic acid is a well-known and intensively studied ingredient for tyrosinase inhibition. However, KA is not stable, is less sufficient in inhibiting tyrosinase activity, and has undesirable side effects. To overcome these adverse effects, researchers have attempted to produce new analogs of KA with higher efficiency in treating hyperpigmentation, acceptable stability, and safety. Various methods have evaluated the efficacy of KA and its derivatives. The findings from these studies revealed that these new agents are effective in treating various skin conditions such as hyperpigmentation and melasma. It was also established that KA derivatives were more efficient in tyrosinase inhibition than KA. Skin lightening agents such as KA have proven to have improved safety profiles for prolonged treatment of skin conditions like melasma, which may be treated using mono or combination therapies. More research on this topic will be supportive in producing safer and efficient agents for tyrosinase inhibition.

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