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A COMPREHENSIVE REVIEW ON A SKIN-BRIGHTENING AGENT KOJIC ACID AND ITS APPLICATIONS

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ABSTRACT
This article reviews the Kojic Acid (KA) as a skin-brightening agent which produced industrially by Aspergillus species in aerobic fermentation and its application in the cosmetics industry. In 1907, Saito discovered KA, a natural product; it has since become one of the most investigated skin-brightening agents. The KA plays an important role in determining certain chemical and physical properties it possesses. KA has different applications in various fields. These days kojic acid performs a vital function, prevention of UV radiation it extensively utilized in whitening creams and lotions because of its anti-tyrosinase activity. It shows other utilization as an anti-inflammatory and analgesic agent in the medical field, an anti-bacterial agent in food industry, and an anti-browning agent for agriculture products. It also has some drawbacks, such as the KA is highly unstable upon exposure air and sunlight it changes its color and the other drawback is cytotoxicity which may be overcome by way of the formation of kojic acid peptides which are more stable. 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: hyperpigmentation, tyrosinase inhibitor, food industry, de-pigmentation, kojic acid, melasma.

INTRODUCTION
In 1907 Saito discovered KA from mycelium of the fungus Aspergillus oryzae grown on steamed rice. Kojic acid originally named as "Koji" which is the name of fungus from which kojic acid derived. Then the name kojic acid was given by Yabuta in 1913. Yabuta also elucidated the structure of kojic acid. On the other hand, a fungal metabolite was introduced as 5-hydroxy-2-hydromethylpyrone [1]. Kojic acid is an organic acid and it is a secondary metabolite secreted by several microorganisms of Aspergillus genus and Penicillium [2, 3]. It can be found naturally in a variety of foods such as soybean paste, soy sauce, and even sake. Kojic acid crystallizes in form of colorless and prismatic needles [4]. It is multifunctional and having weak acidic property. KA has a polyfunctional heterocyclic ring, an oxygen containing backbone & various significant reaction centres that can

undergo additional reactions for example redox, acylation, alkylation, substitution of nucleophilic reactions, substitution of electrophilic reactions, molecular ring opening, & finally chelation together. Kojic acid has several economic uses in various fields. In medical field, kojic acid is used as an anti-bacterial and anti-fungal agent. In the food industries, it has been a food additive for many years working to prevent premature browning of organic food sources [5]. Cosmetically, KA has also been studied as a treatment for wrinkles in the skin because of its known free radical scavenging capabilities [6]. However, the most recognized current use of KA lies in the skin lightening realm of dermatology because of its effectiveness. KA has been used in the treatment of melasma, a predominantly female, idiopathic, hyperpigmentation disorder that occurs mainly on the face [7]. Pregnancy, estrogen exposure, ultraviolet radiation, and family history have all shown some correlation with melasma, but no cause-and-effect relationship has ever clearly been shown [8]. In addition, kojic acid is also used as a chelating agent and activator in insecticide production. In short with the increasing number of industries related to its use in the cosmetics industry interest in kojic acid is increasing [9, 10]. This review describes and discusses the discovery of kojic acid, its potential applications & its properties.

Fungi-Producing Kojic Acid

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 [11]. Some of the species that form this acid include Aspergillus, Penicillium, Acetobacter, and others [12,11,13–15]. Amongst the Aspergillus species, its main producers are Aspergillus oryzae, Aspergillus flavus, and Aspergillus parasiticus [16–19]. It is used in the food and cosmeceutical industries for preserving or changing the color of substances.

The Properties of KA

KA structure plays an important role in determining certain chemical and physical properties it possesses.

- **Physical Properties**

1) Structure of kojic acid is determined as 5-hydroxy-2-hydroxymethyl-δ-pyrone (Fig. 1) [20].
2) Molecular formula of Kojic acid is $C_6H_6O_4$ and molecular weight is 142.11g/mol [21].
3) Kojic acid crystallizes in form of colorless, prismatic needles that sublime under vacuum conditions without any changes.
4) Melting point of kojic acid ranges between 150-160ºC [22, 23, 24].

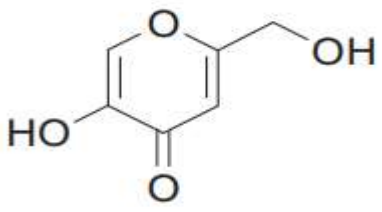

Figure 1. Structure of Kojic acid

- **Chemical Properties**

1) Kojic acid is soluble in polar substances like water, ethanol, ethyl acetate etc. On the contrary, kojic acid is very less soluble in chloroform, ether etc.
2) Kojic acid is classified as multifunctional active quinone-Pyrone with weekly acidic properties.
3) Kojic acid molecule is reactive at every position on a ring.
4) At carbon 5 position hydroxyl (OH-) acts as weak acid, which is capable to form salts with few metals such as Sodium, Zinc, Copper etc which make it more reactive [25].
5) Kojic acid and its derivatives with saccharin molecule are soluble in water.
6) Structure of kojic acid can be modified by glycosylation [26].

7) The side chains of carbon 5 behave as a primary alcohol whose reactivity can be enhanced by the adjacent oxygen atom in the nucleus [27].

Mechanism of Action of Kojic Acid

KA is a kind of secondary metabolite, whose biosynthesis pathway continues to be uncertain to date [28]. However, it is stated that it chelates divalent ions and acts as a tyrosinase inhibitor and a free radical scavenger [29,30]. Chemically kojic acid known as 5-hydroxy 2-hydroxy methyl 4-pyrone and inhibits tyrosinase by copper (Cu^{+2}) chelation at the active spot of the enzyme [31, 32]. Tyrosinase is the rate-limiting enzyme in melanin synthesis and is responsible for converting L-tyrosine to L-3, 4-dihydroxyphenylalanine [33]. It belongs to the type 3 copper-containing protein family, with two copper ions (CuA and CuB) in the active site [34]. 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) [35]. The hypo-pigmenting agent can generally be classified according to which step of melanin production is disrupted. KA is designated as a skin lightening agent that 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 [36]. Historically, tyrosinase inhibitors have proven to be the most effective skin lightening agents.

Besides chelating Cu^{2+} at the active site of tyrosinase, KA has also been shown to bind ions released from other transition metals such as ferric (Fe^{3+}) iron. In one particular study, the chelation of free radicals by KA is showing great promise in combating the appearance of skin aging and wrinkling [6]. However, KA tends to be on the milder end of the skin lightening activity spectrum, as compared with the current standard of care agent, hydroquinone [37]. Decreasing melanogenesis is an effective treatment strategy for the patient with typical hyperpigmentation.

Dosing and Administration

KA can be purchased at the over the counter (OTC) in a 1%-4% concentrated gel or cream [31]. Typically, KA is combined with 2% hydroquinone in an α-hydroxy acid gel matrix. In a recent randomized single-blind comparison study, the melasma area severity index was used to assess the efficacy of varied treatments and that compared KA 1% cream, hydroquinone 2% cream and betamethasone valerate 0.1% cream in patients with melasma. The KA 1% cream used in combination with hydroquinone 2% cream showed higher clinical efficacy than any other composition containing KA 1% cream [38].

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 [12,39]. 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 [12]. 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 [14].

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% [39, 40]. 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 [12,41].

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) [12]. 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 [12].

Adverse Effects of KA

KA, like many topical medications, has the ability to cause local irritation to the original application site. A burning sensation, as well as acneiform rash, occurred in one study after the application of KA 1% cream [38]. It has also been reported that KA can be a strong sensitizer [32, 42]. According to a recent case report, a patient experienced erythematous hyperpigmented areas on the arms and legs that were followed up with a positive patch test to 1% KA [43].

Kojic Acid Derivatives

KA causes skin irritation, has inadequate inhibitory activity, and is not stable during storage, thus reducing its use in cosmetic products [44, 45]. To overcome these disadvantages, many derivatives of KA have been produced [46]. 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 [44]. 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 [44].

Recently, methods for the synthesis of a variety of KA derivatives, such as KA di-palmitate, KA ester, and KA laureate, have been reported [47]. KA peptides have also been investigated as potent tyrosinase inhibitors [48].

There are some potent developed derivatives of kojic acid listed below:

a) Chlorokojic Acid

Chlorokojic acid can be synthesized by simply a chlorination of the 2-hydroxymethyl moiety of kojic acid molecule using thionyl chloride ($SOCl_2$) at room temperature forms chlorokojic acid, with the ring hydroxyl being unaffected. Reaction of kojic acid molecule with thionyl chloride is given below [44,49].

b) Allomaltol

Reduction of chlorokojic acid with zinc dust in concentrated hydrochloric acid results in the production of allomaltol. It is two steps reaction after synthesis of kojic acid [44,49].

c) Iodokojic acid

Iodokojic acid is prepared from chlorokojic acid by treatment with potassium iodide in acetone [44].

d) Fluorokojic acid

Flurokojic acid can be synthesized by treatment of any chlorokojic acid with various metal fluorides such as mercuric fluoride, silver fluoride etc [44].

e) Comenic acid

Comenic acid is prepared by simply an oxidation of kojic acid molecule. Oxidation reaction is given below [49].

f) Pyromeconic acid

Synthesis of pyromeconic acid is one step further of comenic acid making from kojic acid molecule. It can be synthesized by decarboxylation of carboxyl group located at 5 positions of comenic acid [49].

g) 2-Substituted Aryl (Indolyl) Kojic Acid

2-substituted aryl (Indolyl) kojic acid can be synthesized by coupling of iodole, aldehyde and kojic acid using catalytic amount of Indium chloride. Another approach is to use kaolin and Ag nanoparticles as reusable catalyst [50,51].

h) Vanillin-Kojic Acid Ligand
Vanillin-Kojic acid ligand is designed by adding vanillin molecule in linker which makes strong ligand with two kojic acid molecules which is powerful chelator of iron (III) and aluminium (III) (Fig. 17) [52].

i) Bis (Maltolato) Oxovanadium (IV)
BMOV can be synthesized by complexation of maltol with vanadyl sulphate in refluxing aqueous solution, adjusting pH 8.5 using KOH [53].

j) Bis ((5-Hydroxy-4-Oxo-4H-Pyran-2-Yl) Methyl-2-Hydroxy-Benzoatato) Oxovanadium
Bis ((5-hydroxy-4-oxo-4H-pyran-2-yl) methyl-2-hydroxy-benzoatato) oxovanadium or BBOV can be prepared by adding vanadyl sulphate drop-wise in aqueous solution containing (5- hydroxy-4-oxo-4H-pyran-2-yl) methyl benzoate which is made by dissolving chlorokojic acid and sodium benzoic acid in DMF [54].

Biological Activities of Kojic Acid
The available literature indicates that this ingredient has various biological activities, and they are listed below.

1) Antibacterial and Antimicrobial Activity
KA has antifungal and antibacterial properties [55]. Preceding antimicrobial activity assays showed that KA was more active against Gram-negative bacteria than against Gram-positive bacteria [44]. However, some of its derivatives have shown conflicting effects distinct from KA's antibacterial activity [44]. When used in cosmetic products, KA can prevent the growth of microorganisms and can be used as a preservative [56]. 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 [57]. When tested against various microorganisms, KA was most active against Micrococcus luteus and least active against Pseudomonas aeruginosa [57]. In addition, kojic acid in the form of azidometalkojates also shows antibacterial and antifungal effects on several species of Bacillus, Staphylococcus, Saccharomyces, Aspergillus, Rhizopus and Fusarium.
Due to its antifungal properties, KA is incorporated into some antifungal products to improve their effectiveness [57]. Furthermore, it could be useful in treating various fungal infections of the skin as well as yeast infections, ringworm, athlete's foot, and candidiasis [57]. KA and its derivatives have potent activity against bacteria such as Staphylococcus aureus [15]. 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.

2) Antioxidant Activity
KA has anti-oxidant properties [58] and is used as a substitute for hydroquinone (HQ) for skin lightening by the cosmeceutical industry [44,59]. Studies by Zhang et al., (2017) showed that KA improved oxidative stress response in fungi, thus showing the anti-oxidant ability of this metabolite [59]. Other preceding bioactivity studies on KA revealed that it has anti-oxidant properties [57]. 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 [60].

3) Anti-Inflammatory Activity
KA may exert slight anti-inflammatory effects that may favorably improve by subsequent derivation of chosen KA derivatives [61]. 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 a hydrophobic part [62]. A study assessed the anti-inflammatory activity of KA and p-coumaric acid and revealed that both possessed anti-inflammatory properties [59].
In another study, KA and its two novel derivatives were isolated from the fungus Aspergillus versicolor and evaluated for their anti-inflammatory effects [63], showing that KA has a moderate anti-inflammatory effect, while the derivatives 1 and 2 were found to have improved effects [63].

4) Tyrosinase Inhibition Activity

KA is regarded as one of the best skin-lightening agents in the beauty industry [44]. It exerts a slow and effective reversible inhibition of tyrosinase, thus preventing melanin formation, and also plays an important role in cellular melanin formation [44]. According to available data from various studies, it can be used as a monotherapy or combined with other agents [64]. In Japan, this ingredient is known as a quasi-drug [39]. Due to its ability to inhibit tyrosinase activity, KA has been used in several studies as a standard [44].

The Applications of Kojic Acid

Kojic acid has many applications and economic uses in various fields are discussed below:

- **Cosmetic Applications of Kojic Acid**

Nowadays, kojic acid is a popular ingredient in market is in the cosmetic industry in which it plays key role in skin care treatments [65]. Kojic acid has the ability to prevent ultra-violet radiation and inhibit tyrosinase activities which cause pigmentation used as a topical treatment for skin conditions such as spots, melasma, and patches of light brown color resulting from post-inflammatory hyperpigmentation [66, 67]. Intercalation of kojic acid in hydrotalcite-like compounds in order to stabilize kojic acid and to reduce its photo lability which is very effective in melanin synthesis inhibition for skin treatment [68]. At present, kojic acid is primarily used as the basic ingredient for excellent skin lightener in cosmetic creams, where it is used to block the formation of pigment by the deep cells on the skins [14]. Since the incident of skin cancer is increasing rapidly due to exposure towards high ultraviolet radiation of sunlight, currently, this acid is also widely used in cosmetic industry as a skin protective lotion.
KA also enhances the shelf life of cosmetic products through its preservative properties [69]. 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 [15]. Kojic acid loaded nanotechnology-based drug delivery systems can modulate drug permeation through the skin and improve the drug activity for the treatment of skin aging [6]. Hydroquinone has been banned for cosmetic usage in Asia, and it is noted as a possible carcinogenic compound by the Food and Drug Authority (FDA) of USA. This has led to a significant increase in the use of kojic acid as a replacement for hydroquinone that bleaches and possibly damages skins in cosmetic products.

- **In the medical field**

Kojic acid is widely used in medicinal and cosmetic formulations as a skin-lightening agent based on its de-pigmenting activity. Kojic acid is used as a pain killer and anti-inflammation drug [70]. Kojic acid and its peptide derivatives has also been reported as potential antibacterial agents [71]. Among them, 7-iodo kojic acid has the most potent activity against staphylococcus aureus. The factor that enhances the anti-microbial activity is attributable to the high hydrophobicity of the substituent at the end 7 position. Emami S et al. in [72] found novel mannich bases of 7-piperazinylquinolones with kojic acid and chlorokojic acid showed significant effect as antibacterial agents.
Kojic acid derivative, O3-Acyl kojic acid as a potent and selective human neutrophil elastase inhibitor for the treatment of chronic and acute inflammatory lung diseases [73]. New bis- kojic derivatives induced faster clearance from main organs as compared with the mono- meric analog. So kojic acid could be applied as aluminium chelating agent in the treatment of aluminium related diseases [74]. Kojic acid can be used as antioxidant iron chelator for topical treatment of wound healing [75].

- **In food industry**

kojic acid is used as an agent to prevent undesirable melanosis (blackening) of agricultural products such as vegetables, fruits and crustaceans during storage. Not only that, kojic acid also acts as a precursor for flavour enhancers (that is, maltol and ethyl maltol). Kojic acid has the ability to inhibit the action of polyphenol oxidase (PPO) enzyme when these products are exposed to oxygen and reduce of o-quinones to diphenols to prevent the formation of the final pigment (melanin) or the combination of the above actions [76]. Apart from that, it is also used as an 'anti- speck' agent in raw noodles during production processes. This is to avoid the color changes and black spot formation on noodles by inhibiting the tyrosinase enzyme [77]. Anti-bacterial activity of kojic acid grafted chitosan oligosaccharide derivative that supports for developing new antimicrobial agents and explore the scope of application of kojic acid in food industries [78]. Metal complex of Kojic acid–phenylalanine inhibits mushroom tyrosinase activity as much as Acid–phenyl alanine and reduce melanin contents in melanocyte efficiently [79].

- **In the chemical industry**

Kojic acid is recognised as an important intermediate in the production of chemicals that can be used as pharmaceuticals. Novotny et al. (1999) claimed that kojic acid could be used in the preparation of compounds with an anti-neoplastic potential [80]. In addition, the antineoplastic activity of kojic acid derivatives is based on various mechanisms of actions on different levels of cellular metabolism and functions, which make this compound useful as a cytotoxic agent.

Kojic acid can be used as an analytical tool for ion determination since the reaction of kojic acid with the trace of ferric ion can form deep red complex [81]. Metal chelates of kojic acid have been advocated as the source materials giving the controlled release of metallic ions in curing agents or catalysts [82]. Kojic acid also has been used as a substrate for chemicals synthesis of comenic acid and 2- methyl-4-pyrone [83]. Comenic acid is an important intermediate for the synthesis of maltol and its derivative, while 2-methyl-4-pyrone is a compound which is normally associated with natural pigments. Szklarzewicz J et al. [84] found novel chemical complexes of Mo (IV) in reaction with compounds maltol, ethyl maltol and kojic acid.

- **In agriculture**

Kojic acid is widely used in agriculture as a chelating agent and insecticide activator for insecticide production. Newly designed two ligands composed of vaniline and O-vaniline molecules, each molecule with two kojic acid molecules joined with methylene group which have been proved as powerful chelators of iron and aluminium [85].

CONCLUSION

The present report opened a new window for the researchers to start their work on Kojic acid which is a well-known and intensively studied ingredient for tyrosinase inhibition. Kojic acid is mainly secreted by more than 58 Aspergillus fungal strains and Aspergillus flavus produces a large amount of kojic acid by using yeast extract & glucose as nitrogen & carbon sources respectively. It is widely used in the food field as well as medical research practice. In addition to medical use, it is also shows antioxidant & tyrosinase inhibitory properties, antibacterial and antifungal effects. A very low dose of kojic acid of about 1% to 3% is more effective in depigmentation of the skin. But KA 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. 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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