Kojic Acid: A Comprehensive Review

Farah Bashir[1], Kishwar Sultana [1,] Maryam Khalid[1] ,Hafiza Rabia , Najm ul Hassan Khan[,*2]

[1] Department of Pharmacy, The University of Lahore, Pakistan
[*2]M.Islam College of Pharmacy,Gujranwala, Pakistan
*najambaloch@gmail.com

Abstract:

Due to the emerging nature of kojic acid, current project was conducted to introduce the abilities in details. KA is produced industrially by Aspergillus species in aerobic fermentation. Its structure was identified as 5-hydroxymethyl--pyrone. The KA plays an important role in determining certain chemical and physical properties it possesses. KA has different applications in various fields. It is broadly utilized in cosmetics, medicine, food, agriculture, chemical and other industries. These days kojic acid performs a vital function in cosmetics specifically skin care products because it enhances the capability to prevent UV radiation it extensively utilized in whitening creams and lotions because of its anti tyrosinase activity. Kojic acid keeps getting hold on attention because of its economic potential as an anti-inflammatory and analgesic agent in the medical field. KA is utilized as an anti-bacterial agent in food industry & because of its antioxidant activity it is utilized as an anti-browning agent for agriculture products. Due to various uses of organic molecules the demand for kojic acid has rapidly increased. 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.

Keywords:

kojic acid, tyrosinase inhibitor, food industry, fungicide, anti-inflammatory, radio protective

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 also consumed in the food and it is believed to be beneficial to health in Japan. Kojic acid can be produced by variety of microorganisms under various aerobic conditions by various carbohydrate sources & its lethal dose in living things is about 1g/kg [2]. KA has a polyfunctional heterocyclic ring, an oxygen containing backbone & various significant reaction centers that can undergo additional reactions for example redox, acylation, alkylation, substitution of nucleophilic reactions, substitution of electrophilic reactions, molecular ring opening, & finally chelation together.

Protocols for the fermentation procedure making use of diverse carbohydrates containing media & the CCM-F-780 or the CCM-F-781 kojic acid generating mutant strains have been recognized & the new information on kojic acid production through fermentation has been reported[3]. The fermentation process involving several steps starts with the inoculation medium for kojic acid producing microorganisms to produce kojic acid as a pale yellow, yellow prismatic needle. Since 1955 the kojic acid market has been established for about 40 years. Pfizer & American companies announced their 1st try to produce its organic acid. The company has obtained a method for producing kojic acid and its recycling and a method for preparing a derivative used as a pesticide. In short with the increasing number of industries related to its use

in the cosmetics industry interest in kojic acid is increasing [4, 5].

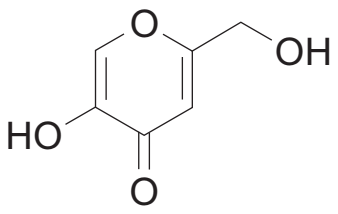
Although kojic acid has been produced and used in industry since decades and it is still widely studied. It is generally believed that the two main areas are those that are associated with the development of the strain & those that are associated with the fermentation process development. Kojic acid is produced by Aspergillus spp. & Penicillium spp. mainly belonging to the flavus oryzaetamarii group. According to reports A. flavus [6] A. oryzae [7, 8], A. tamarii [9] and A. parasiticus [10, 11] have the capability to provide a huge quantity of kojic acid. Although numerous possible KA producing strains have been isolated but little attention has been paid to the improvement of strains by mutation or genetic engineering techniques. This review describes and discusses the discovery of kojic acid, its potential applications & its properties.

The Properties of KA

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

Physical Properties

- The KA structure was determined to be 5-hydroxy-2-hydroxymethyl-δ-pyrone (Fig. 1) [12]
- KA has melting point between 151 C⁰ and 154 C⁰ [13].
- The molecular formula of the cookie acid is $C_6H_6O_4$ the molecular weight is 142.1 and it is determined by the freezing point method [14].
- Kojic acid crystallizes as a colourless prismatic pin and sublimates under vacuum without any change [15].



Kojic acid

Figure 1. Structure of Kojic acid

Chemical Properties

- It is soluble in ethanol, water, ethyl acetate and other polar substances. On the contrary the solubility of kojic acid in chloroform, ether, and the like is extremely poor.
- Kojic acid is classified as having a weekly acidic polyfunctional active quinone-pyrone.
- The kojic acid molecule is reactive at every site on the ring.
- In the carbon 5 position hydroxyl (OH-) acts as a weak acid which can produce salts with a small amount of metal, such as sodium, zinc, copper, etc., making it more hydrophilic.
- Aspergillus acid and its derivatives with saccharin molecules are soluble in water.
- The structure of kojic acid can be modified by glycosylation [16].
- The side chain of carbon 5 behaves as a primary alcohol, and its reactivity can be enhanced by adjacent oxygen atoms in the core [1].

The Applications of Kojic Acid

Fields	Functions	References
Medical	Antibacterial Antifungal analgesic	17, 18 19, 1
Food	Flavor enhancers Antioxidant Maltol and Ethyl maltol	20 21, 22 23, 24
Agriculture	Anti melanosis Insecticide activator	2 2 2 5, 26 27 28,
Cosmetic	Whitening agent UV filter Tyrosinase inhibitor Radical scavenging activity Radio protective agent	29 30 4 13 31, 2 9, 32
Chemistry	Iron determination reagent 2-methyl-4-pyrone Iron chelator synthesis Conjugates of Kojic acid-chitosan	3 3, 3 4, 35 36,

Table 1: Applications of kojic acid Antibacterial

In Cosmetic Industry

The most significant benefits of kojic acid are in the cosmetics and healthcare industry. It is mainly used as an essential material for the skin whitening creams production, skin care lotions,

whitening soaps & dental care products. It acts as UV protectant & inhibits the melanin production by inhibiting the tyrosinase formation, the enzyme which is liable for skin pigmentation so inhibiting hyper pigmentation of human skin[13],[31].

Mechanism of Action

Chemically referred to as 5-hydroxy 2-hydroxy methyl 4-pyrone. KA inhibits tyrosinase by copper (Cu^{+2}) chelation at the effective spot[37],[38] of the enzyme. Tyrosinase is the rate-limiting enzyme in melanin synthesis and is responsible for converting L-tyrosine to L-3,4-dihydroxyphenylalanine[39]. The low pigmenting agent can generally be classified according to which step of melanin production is disrupted. They depend on the agents that can act before, during, or after melanin production. KA is designated as a skin lightening agent that acts during the actual synthesis of melanin. Historically, tyrosinase inhibitors have proven to be the most effective skin lightening agents.

Dosing and Administration

KA can be purchased at the over-the-counter (OTC) with a 1%-4% concentrated gel or cream. Usually, 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 evaluate the efficacy of different treatment methods. This study compared KA 1% cream hydroquinone 2% cream and E.C. 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[40].

Adverse Effects of KA

Like many topical drugs, KA has the ability to cause local irritation to the original application site. A burning sensation and acne-like rash occurred in a study after the use of KA 1% cream [40]. According to reports, KA may be a strong sensitizer [38], [39]. According to a recent case report, one patient had erythema hyper perfusion in the arms and legs, followed by a 1% KA positive patch test [41].

Anti-Inflammatory and Antineoplastic Properties of KA derivatives

It has been shown that KA can apply a minor anti-inflammatory effect which can be favorably improved by the successive derivatization of the selected derivative of kojic acid. While looking for new compounds' antitumor activity the impact of kojic acid halogen derivatives on the propagation of leukemia L-1210 cells & pituitary GH4C1 tumor cells was examined. It was stated for the first time that a group of numerous halogen derivatives of 5-hydroxy-2-hydroxymethyl-4- pyrone may be capable medications with anti-leukemia activity [42] the role of pyrone derivative is not because of the metal ion chelating capacity. 2 halogen derivative of kojic acid 5-hydroxy-2-chloromethyl-4-pyrone and 5-hydroxy-2-hydroxymethyl-4-pyrone were found to inhibit DNA, RNA & protein synthesis [43]. It was found that 2.6um of 5-benzyloxy-2-thiocyanatomethyl 1-4- pyrone significantly inhibited tumor cell growth and inhibited DNA synthesis and cytoplasm phosphorylation [44]. In addition the anti-tumor cytotoxic effects of selected azidomethyl alkanoates (Cu, Zn, Mn, Mg and Ni) salts were estimated on Hela cells & the maximum resistance was confirmed by azide Z-salts tumor effects [45].

Kojic Acid in Food

The *Aspergillus flavus* group is traditionally used to produce many foods, including miso (fermented soya bean paste), soy sauce & sake. KA is extensively utilized as food additive to prevent enzymatic browning in the food industry, & KA is used as an agent to prevent undesired blackening of agricultural products such as vegetables, fruits & crustaceans during storage. KA has the ability to inhibit the action of polyphenol oxidase enzymes when these products are exposed to oxygen [46]. In addition, it is utilized as anti-seed agent in raw noodles

during the production process. This is to avoid color change & black dot formation on the noodles by tyrosinase inhibition [47,48].

Radio Protective Effects of Kojic Acid

Kojic acid stimulates lymphocyte proliferation, enhances neutrophil function and removes increased reactive oxygen species from leukocytes in the blood. Recent studies have shown that taking kojic acid 24 hours before gamma irradiation can reduce the useful biological properties of kojic acid, safe consumption of food, and radiation protection in recent studies. This study evaluated the lethal dose of gamma. The mice were irradiated with kojic acid for 1 hour before irradiation and compared with amifostine as a radio protective drug and antioxidant activity. A single administration of a natural compound kojic acid prior to gamma irradiation reduces the mortality caused by irradiation. Maximum protection was observed at a dose of 350mg/kg kojic acid 1 hour before irradiation, and it had similar protective efficacy as the amifostine at a dose 1 hour before irradiation and it had similar protective efficacy as the amifostine at a dose of 200mg/kg [49].

KA Scavenges Free Radicals While Potentiating Leukocyte Functions

KA significantly reduces the level of ROS producing by neutrophils and cellular ROS production systems. It significantly enhances the phagocytosis of neutrophils. Furthermore, the concentration of calcium in human neutrophils increases in KA presence. These consequences indicate that KA is advantageous in terms of host defense because it improves many activities of leukocytes but eliminates ROS that are extremely released from cells or formed in tissues or blood vessels that may be harmful to tissues of host. [29]

Antifungal Activity of Kojic Acid

The antifungal action of KA on therapeutically vital fungi was assessed. Trichophyton rubrum & Candida albicans are significant human pathogenic fungi that cause numerous human fungal diseases for example hoof foot, nail file, & cutaneous candidiasis. Cryptococcus neoformans is a yeast-like fungal pathogen which causes immunocompromised individuals, especially fatal meningitis in AIDS patients [50]. In Cryptococcus neoformans, melanin producing bacteria are known to have melanin associated with their virulence [51]. It has been reported that melanin formation is involved in reducing the sensitivity and enzyme degradation of Cryptococcus neoformans to heat and heat and cold [52]. In this investigation, we assessed the impact of kojic acid on melanin formation by Cryptococcus neoformans and the sensitivity of antifungal-agents. The results displayed that KA significantly decreased the melanization of Cryptococcus neoformans at sub-MIC values. In Cryptococcus neoformans, melanin production is the main virulence factor because melanin-deficient mutants lose virulence & the conversion of the melanin phenotype restores virulence [53]. In Wangiella dermatitis, the pathogenic effect of fungal melanin-deficient strains on mice is diminished [18]. It has been suggested that melanin may help protect Cryptococcus neoformans from the host immune system by removing leukocyte antibacterial oxidants [54]. Therefore, these facts indicate that melanin synthesis inhibitors in melanin-producing bacteria may be probable targets for antifungal agents, comparable to melanin inhibitors such as tricyclazole and pyroquinoline, for preventing the pathogen caused by the plant pathogen Magnaporthe grisea rice blast. In this investigation, our results may provide the possibility of KA inhibiting melanin production & have the opportunity to diminish the virulence of Cryptococcus neoformans.

Kojic Acid in Agriculture

KA is widely utilized as a chelating agent & insecticide activator for pesticide production in agriculture. The newly designs two ligands consisting of vaniline and o-vaniline molecules, each containing two kojic acid molecules links to methylene groups have been shown to be potent iron and aluminum chelators [55].

Kojic Acid as Anti-diabetic Agent

The combination of kojic acid and vanadium enhances its efficacy and safety as an anti-diabetic agent. The effect of kojic acid derivative on double maltol vanadyloxynitride on streptozocin induced diabetic rats effectively reduced blood glucose levels indicating that it can be used as an effective and safe anti diabetic agent [56]

Drawbacks Of Kojic acid

Kojic acid has two disadvantages, one is cytotoxicity and the other is storage instability.

However, due to the limitations in finding clinically proven safe & effective cosmetic formulations, synthetic molecules are now being designed to test & outperform traditional molecules. Recently peptides have emerged as more effective cosmetic agents containing a large number of individually molecules.

Kojic acid peptides

In the present investigation, Kojic acid peptides were synthesized and investigated its role in order to overcome the limitations of KA.h

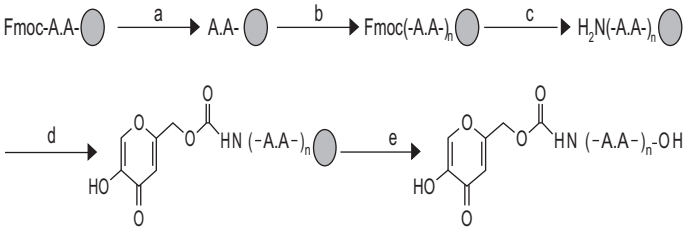


Figure 2: Synthesis of kojic acid peptides

Reagents & Conditions

- Treat with 2% 1,8- diazabicyclo undec-7-ene in N, N-dimethyl formamide (DMF) for 10min.
- Mixed Fmoc-A.A2OH hydroxy benotriazole and diisopropylcarbodiimide with resin for 2 hours.
- Repeat procedure 1 & 2.
- React with KA imidazole HOBt DMF for overnight
- React with reagent Tri fluoroacetic acid/ thio anisole/ phenol/ water/ ethane dithiol (82.5/5/5/5/2.5) (v/v) for 1 hour & treat with pre cooled diethyl ether.

The most extreme tyrosinase activity was estimated by kojic acid peptides. Therefore, the KA peptides were exposed to melanin assay, cytotoxicity assay & the stability of kojic acid peptides was finally determined. It was seen that this newly synthesized kojic acid peptide stability & effectively inhibits tyrosinase activity & melanin content of B16f10 mouse melanoma cells without showing cytotoxicity [57].

Conclusion:

The present report opened a new window for the researchers to start their work keeping in view of this review. Kojic acid is mainly secreted by more than 58 Aspergillus fungal strains. Aspergillus flavus produces a large amount of kojic acid by using yeast extract & glucose as nitrogen & carbon sources respectively. KA is safe for humans & because of its antioxidant & tyrosinase inhibitory properties it is widely used in the food field as well as medical research practice. In addition to medical use it is also shows effective antibacterial and antifungal effects. More than 150 Kojic acid derivatives have been identified as bio pesticides and bio bactericides in agricultural sector. A very low dose of kojic acid of about 1% to 3% is more effective in depigmentation of the skin. In addition research in these areas will help improve human resistance to microbial infections and diseases such as cancer.

References:

01- Beélik, A. in Advances in carbohydrate chemistry Vol. 11 145-183 (Elsevier, 1956).

02- Bajpai, P., Agrawal, P. & Vishwanathan, L. KOJIC ACID-SYNTHESIS AND PROPERTIES. Journal of Scientific & Industrial Research 41, 185-194 (1982).

03- Balint, S., Forsthoffer, J., Brtko, J. & Dobias, J. Enlargement of yield of kojic acid production. CS Patent (1988).

04- Bentley, R. From miso, sake and shoyu to cosmetics: a century of science for kojic acid.

Nat. Prod. Rep. 23, 1046-1062 (2006).

05- Brtko, J. et al. Kojic acid and its derivatives: history and present state of art. Central european journal of public health 12, S16-S17 (2004).

06- Basappa, S., Sreenivasamurthy, V. & Parpia, H. Aflatoxin and kojic acid production by resting cells of Aspergillus flavus Link. Microbiology 61, 81-86 (1970).

07- Kwak, M. Y. & Rhee, J. S. Cultivation characteristics of immobilized Aspergillus oryzae for kojic acid production. Biotechnology and bioengineering 39, 903-906 (1992).

08- Takamizawa, K. et al. Optimization of kojic acid production rate using the Box-Wilson method. Journal of fermentation and Bioengineering 82, 414-416 (1996).

09- Gould, B. S. The metabolism of Aspergillus tamarii Kita. Kojic acid production. Biochemical Journal 32, 797 (1938).

10- Nandan, R. & Polasa, H. Inhibition of growth of kojic acid biosynthesis in Aspergillus by some chlorinated hydrocarbons. Indian J. Microbiol 25, 21-25 (1985).

11- Coupland, K. & Niehaus Jr, W. G. Effect of nitrogen supply, Zn2+, and salt concentration on kojic acid and versicolorin biosynthesis by Aspergillus parasiticus. Experimental mycology 11, 206-213 (1987).

12- Kitada, M. Studies on kojic acid fermentation. VI. Production and recovery of kojic acid on an industrial scale. Hakkokogaku 49, 343-349 (1971).

13- Ohyama, Y. Melanogenesis-inhibitory effect of kojic acid and its action mechanism. Fragrance J. 6, 53-58 (1990).

14- WILSON, B. J. Miscellaneous aspergillus toxins. Microbes toxins, fungal toxins, 235-250 (1971).

15- Saito, K. Über die Säurebildung bei Aspergillus Oryzœ. Shokubutsugaku Zasshi 21, 7-11 (1907).

16- Nakajima, N., Ishihara, K. & Hamada, H. Functional glucosylation of kojic acid and daidzein with the Eucalyptus membrane-associated UDP-glucosyltransferase reaction system. Journal of bioscience and bioengineering 92, 469-471 (2001).

17- Kotani, T., Ichimoto, I., Tatsumi, C. & Fujita, T. Bacteriostatic activities and metal chelation of kojic acid analogs. Agricultural and Biological Chemistry 40, 765-770 (1976).

18- Kayahara, H. et al. Amino acid and peptide derivatives of kojic acid and their antifungal properties. Agric. Biol. Chem. 54, 2441-2442 (1990).

19- Baláž, Š. et al. Biologically important physicochemical properties of kojic acid derivatives. Collection of Czechoslovak chemical communications 58, 693-701 (1993).

20- Wood, B. J. Microbiology of fermented foods. (Springer Science & Business Media, 2012).

21- Burdock, G. A., Soni, M. G. & Carabin, I. G. Evaluation of health aspects of kojic acid in food. Regulatory toxicology and pharmacology 33, 80-101 (2001).

22- Chen, J. S. et al. Inhibitory effect of kojic acid on some plant and crustacean polyphenol oxidases. Journal of Agricultural and food

Chemistry 39, 1396-1401 (1991).

23- Niwa, Y. & Miyachi, Y. Antioxidant action of natural health products and Chinese herbs. Inflammation 10, 79-91 (1986).

24- Tatsumi, C., Ichimoto, I., Uchida, S. & Nonomura, S. Production of comenic acid from kojic acid by microorganism. JOURNAL OF FERMENTATION TECHNOLOGY 47, 178-& (1969).

25- Saruno, R., Kato, F. & Ikeno, T. Kojic acid, a tyrosinase inhibitor from Aspergillus albus. Agricultural and Biological Chemistry 43, 1337-1338 (1979).

26- Buchta, K. Organic acids of minor importance in biotechnology biomass, microorganisms for special application, microbial products, energy from renewable resources. Bioehringer, Ingelheim Federal Republic of Germany 447 (1982).

27- Dowd, P. F. Toxicological and biochemical interactions of the fungal metabolites fusaric acid and kojic acid with xenobiotics in Heliothis zea (F.) and Spodoptera frugiperda (JE Smith). Pesticide Biochemistry and Physiology 32, 123-134 (1988).

28- Dobias, J., Nemec, P. & Brtko, J. The inhibitory effect of kojic acid and its two derivatives on the development of Drosophila melanogaster [insecticidal effect]. Biologia (1977).

29- Niwa, Y. & Akamatsu, H. Kojic acid scavenges free radicals while potentiating leukocyte functions including free radical generation. Inflammation 15, 303-315 (1991).

30- Masse, M. O., Duvallet, V., Borremans, M. & Goeyens, L. Identification and quantitative analysis of kojic acid and arbutine in skin-whitening cosmetics. International journal of cosmetic science 23, 219-232 (2001).

31- Noh, J.-M. et al. Kojic acid–amino acid conjugates as tyrosinase inhibitors. Bioorganic & medicinal chemistry letters 19, 5586-5589 (2009).

32- Emami, S., Hosseinimehr, S. J., Taghdisi, S. M. & Akhlaghpoor, S. Kojic acid and its manganese and zinc complexes as potential radioprotective agents. Bioorganic & medicinal chemistry letters 17, 45-48 (2007).

33- HASIZUME, K., YAMAMURA, S. & INOUE, S. A convenient synthesis of 2-methyl-4-pyrone from kojic acid. Chemical and Pharmaceutical Bulletin 16, 2292-2296 (1968).

34- Mitani, H., Koshiishi, I., Sumita, T. & Imanari, T. Prevention of the photodamage in the hairless mouse dorsal skin by kojic acid as an iron chelator. European journal of pharmacology 411, 169-174 (2001).

35- Guibal, E. Interactions of metal ions with chitosan-based sorbents: a review. Separation and purification technology 38, 43-74 (2004).

36- Synytsya, A. et al. Conjugation of kojic acid with chitosan. Carbohydrate polymers 72, 21-31 (2008).

37- Davis, E. C. & Callender, V. D. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. The Journal of clinical and aesthetic dermatology 3, 20 (2010).

38- Draelos, Z. D. Skin lightening preparations and the hydroquinone controversy.

Dermatologic Therapy 20, 308-313 (2007).

39- Goldstein, B. G., Goldstein, A. O. & Callender, V. D. Learn how UpToDate can help you.

40- Deo, K. S., Dash, K. N., Sharma, Y. K., Virmani, N. C. & Oberai, C. Kojic acid vis-a-vis its combinations with hydroquinone and betamethasone valerate in melasma: a randomized, single blind, comparative study of efficacy and safety. Indian journal of dermatology 58, 281 (2013).

41- García-Gavín, J., González-Vilas, D., Fernández-Redondo, V. & Toribio, J. Pigmented contact dermatitis due to kojic acid. A paradoxical side effect of a skin lightener. Contact Dermatitis 62, 63-64 (2010).

42- Bransová, J., Brtko, J., Uher, M. & Novotný, L. Antileukemic activity of 4-pyranone derivatives. The international journal of biochemistry & cell biology 27, 701-706 (1995).

43- Bransova, J., Uher, M. & Brtko, J. Regulation of selected biological processes in neoplastic cell lines by halogen derivatives of 5-hydroxy-2-hydroxymethyl-4-pyranone. Anticancer research 18, 4423-4428 (1998).

44- Bransova, J., Uher, M., Novotny, L. & Brtko, J. 5-benzyloxy-2-thiocyanatomethyl-4-pyranone, a novel heterocyclic compound: synthesis, structure determination and effects on neoplastic cell growth. Anticancer research 17, 1175-1178 (1997).

45- Hudecová, D., Jantová, S., Melník, M. & Uher, M. New azidometalkojates and their biological activity. Folia microbiologica 41, 473-476 (1996).

46- Son, S., Moon, K. & Lee, C. Inhibitory effects of various antibrowning agents on apple slices. Food Chemistry 73, 23-30 (2001).

47- Kaatz, H., Streffer, K., Wollenberger, U. & Peter, M. G. Inhibition of mushroom tyrosinase by kojic acid octanoates. Zeitschrift für Naturforschung C 54, 70-74 (1999).

48- Uchino, K., Nagawa, M., Tonosaki, Y., Oda, M. & Fukuchi, A. Kojic acid as an anti-speck agent. Agricultural and biological chemistry 52, 2609-2610 (1988).

49- Hosseinimehr, S. J., Emami, S., Zakaryaee, V., Ahmadi, A. & Moslemi, D. Radioprotective effects of kojic acid against mortality induced by gamma irradiation in mice. Saudi medical journal 30, 490-493 (2009).

50- Jimbow, K. & Minamitsuji, Y. Topical therapies for melasma and disorders of hyperpigmentation. Dermatologic Therapy 14, 35-45 (2001).

51- Ambrogi, V. et al. Immobilization of kojic acid in ZnAl-hydrotalcite like compounds. Journal of Physics and Chemistry of Solids 73, 94-98 (2012).

52- Gonçalez, M., Correa, M. A. & Chorilli, M. Skin delivery of kojic acid-loaded nanotechnology-based drug delivery systems for the treatment of skin aging. BioMed research international 2013 (2013).

53- Öztürk, G., Erol, D. D., Uzbay, T. & Aytemir, M. D. Synthesis of 4 (1H)-pyridinone derivatives and investigation of analgesic and antiinflammatory activities. Il Farmaco 56, 251-256 (2001).

54- Emami, S. et al. Mannich bases of 7-piperazinylquinolones and kojic acid derivatives: Synthesis, in vitro antibacterial activity and in silico study. European journal of medicinal chemistry 68, 185-191 (2013).

55- Nurchi, V. M. et al. Kojic acid derivatives as powerful chelators for iron (III) and aluminium (III). Dalton transactions 40, 5984-5998 (2011).

56- Wei, Y., Zhang, C., Zhao, P., Yang, X. & Wang, K. A new salicylic acid-derivatized kojic acid vanadyl complex: synthesis, characterization and anti-diabetic therapeutic potential. Journal of inorganic biochemistry 105, 1081-1085 (2011).

57- Singh, B. K. et al. Kojic acid peptide: a new compound with anti-tyrosinase potential. Annals of dermatology 28, 555-561 (2016).