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Literature Review on the Effectiveness of Kojic Acid in Reducing Skin Hyperpigmentation

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Abstract

Skin hyperpigmentation is a common dermatological condition characterized by excessive melanin production or abnormal melanin distribution, frequently induced by ultraviolet radiation, inflammation, aging, or hormonal changes. Kojic acid, a naturally derived fungal metabolite, has gained widespread attention as a topical depigmenting agent because of its ability to inhibit tyrosinase, the key enzyme involved in melanogenesis. This systematic literature review aimed to evaluate the effectiveness and safety of kojic acid in reducing skin hyperpigmentation. The review was conducted according to the PRISMA 2020 guidelines using publications retrieved from PubMed, Scopus, Web of Science, and Google Scholar. Eligible studies included clinical, experimental, and preclinical investigations evaluating kojic acid alone or in combination with other depigmenting agents. Overall, the reviewed evidence demonstrated that kojic acid effectively reduced pigmentation intensity, particularly in melasma and post-inflammatory hyperpigmentation, by suppressing melanin synthesis. Superior outcomes were generally observed when kojic acid was combined with hydroquinone, glycolic acid, niacinamide, or other complementary agents. Although mild adverse effects, including skin irritation and contact dermatitis, were occasionally reported, kojic acid exhibited an acceptable safety profile when appropriately formulated and used. Further standardized clinical trials are needed to optimize its concentration, formulation, and treatment duration.

Keywords Kojic acid; Hyperpigmentation; Melasma; Tyrosinase inhibitor; Melanogenesis; Skin depigmentation.

INTRODUCTION

Skin hyperpigmentation is one of the most prevalent dermatological disorders affecting individuals of various ethnicities and age groups worldwide (Mosca & Morrone, 2023; Yoo, 2022). It is characterized by excessive melanin production or abnormal melanin distribution within the epidermis or dermis, resulting in localized or diffuse darkened areas of the skin. Hyperpigmentation encompasses several

clinical conditions, including melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, freckles (ephelides), and drug-induced pigmentation. Although these disorders are generally benign and do not pose a direct threat to physical health, they often produce substantial psychosocial consequences. Individuals experiencing facial hyperpigmentation frequently report decreased self-confidence, impaired quality of life, emotional distress, and dissatisfaction with their appearance, making effective treatment an important aspect of dermatological care.

Melanin synthesis, known as melanogenesis, is a complex biological process occurring within melanocytes located in the basal layer of the epidermis (Lu et al., 2021). The process is primarily regulated by the enzyme tyrosinase, which catalyzes the hydroxylation of L-tyrosine to L-DOPA and subsequently oxidizes L-DOPA to dopaquinone, initiating a cascade of biochemical reactions leading to melanin formation. Various intrinsic and extrinsic factors influence melanogenesis, including ultraviolet (UV) radiation, hormonal fluctuations, inflammatory mediators, genetic predisposition, oxidative stress, and aging. Among these, chronic UV exposure is considered the most significant environmental trigger because it stimulates melanocyte activity through increased production of melanocyte-stimulating hormone (MSH), endothelin-1, inflammatory cytokines, and reactive oxygen species (ROS), all of which promote excessive pigmentation.

Given the multifactorial nature of hyperpigmentation, numerous therapeutic approaches have been developed to reduce excessive melanin accumulation. These treatments include topical depigmenting agents, chemical peeling, laser therapy, microneedling, and photoprotection (Piętowska et al., 2022). Among topical agents, hydroquinone has long been regarded as the gold standard because of its potent inhibition of tyrosinase activity. Nevertheless, concerns regarding adverse effects such as skin irritation, exogenous ochronosis, contact dermatitis, and potential cytotoxicity have encouraged researchers and clinicians to investigate safer alternatives with comparable depigmenting efficacy. Consequently, naturally derived compounds have attracted considerable scientific interest owing to their favorable safety profiles and antioxidant properties.

One of the most extensively studied natural depigmenting compounds is kojic acid. Kojic acid is a secondary metabolite produced by several fungal species, particularly *Aspergillus oryzae*, *Aspergillus flavus*, and *Penicillium* species during carbohydrate fermentation (Rasmey & Abdel-Kareem, 2021). Initially discovered as a by-product of Japanese rice fermentation, kojic acid has been widely incorporated into cosmetic and pharmaceutical formulations because of its remarkable skin-

lightening properties. Its principal mechanism of action involves chelation of copper ions at the active site of tyrosinase, thereby inhibiting the enzyme responsible for melanin biosynthesis. By suppressing tyrosinase activity, kojic acid effectively reduces melanin formation and gradually lightens hyperpigmented lesions.

Beyond tyrosinase inhibition, emerging evidence suggests that kojic acid exhibits additional biological activities contributing to its depigmenting effects (Phasha et al., 2022; Zilles et al., 2022). Several experimental studies have demonstrated that kojic acid possesses antioxidant properties capable of scavenging reactive oxygen species generated by ultraviolet radiation. Since oxidative stress has been implicated in stimulating melanogenesis through activation of intracellular signaling pathways, antioxidant activity may further enhance the ability of kojic acid to reduce abnormal pigmentation. Furthermore, some investigations indicate that kojic acid may exert anti-inflammatory effects, thereby minimizing melanocyte stimulation following inflammatory skin disorders such as acne vulgaris or eczema, conditions commonly associated with post-inflammatory hyperpigmentation.

Clinically, kojic acid is available in various topical formulations, including creams, serums, gels, lotions, soaps, and chemical peeling preparations. Concentrations generally range from 1% to 4%, depending on the intended therapeutic application and formulation stability (Phasha et al., 2022; Zilles et al., 2022). Kojic acid is frequently combined with other depigmenting agents, including glycolic acid, hydroquinone, arbutin, niacinamide, azelaic acid, vitamin C, retinoids, and corticosteroids. These combination therapies are designed to target multiple pathways involved in melanogenesis, improve treatment efficacy, and shorten the duration required to achieve visible clinical improvement. Several randomized controlled trials have reported superior outcomes for combination regimens compared with monotherapy, although the magnitude of improvement varies considerably among different patient populations and pigmentation disorders.

Despite its widespread application, the clinical effectiveness of kojic acid remains a subject of ongoing investigation. Differences in study design, treatment duration, formulation type, concentration, outcome assessment methods, skin phototype, and underlying causes of hyperpigmentation have generated inconsistent findings across published studies. While many investigations demonstrate significant reductions in melanin index, lesion severity, and pigmentation scores following topical kojic acid therapy, others report only modest clinical improvement or emphasize treatment-related adverse effects such as erythema, irritation, contact dermatitis, and skin sensitivity, particularly with prolonged use or higher

concentrations. Consequently, clinicians require comprehensive evidence synthesizing these findings to determine the optimal role of kojic acid within current hyperpigmentation management strategies (Burnett et al., 2010; Pillaiyar et al., 2017).

Therefore, conducting a comprehensive literature review is essential to critically evaluate the available scientific evidence regarding the effectiveness of kojic acid in reducing skin hyperpigmentation. By systematically reviewing experimental studies, randomized clinical trials, observational research, and relevant review articles, this study aims to summarize current knowledge concerning the efficacy, mechanisms of action, safety profile, therapeutic limitations, and clinical applications of kojic acid. Furthermore, this review seeks to identify existing research gaps, including inconsistencies in treatment protocols, long-term safety data, comparative effectiveness with other depigmenting agents, and opportunities for future investigations. The findings are expected to provide evidence-based recommendations for dermatologists, researchers, cosmetic scientists, and healthcare professionals in selecting safe, effective, and rational topical therapies for patients with hyperpigmentation disorders.

METHODS

This study employed a systematic literature review (SLR) to synthesize and critically evaluate the available scientific evidence regarding the effectiveness of kojic acid in reducing skin hyperpigmentation (Saritas & Topraklikoglu, 2022). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which provide a standardized framework for identifying, screening, selecting, and reporting relevant studies in a transparent and reproducible manner (Page et al., 2021). The review focused on experimental, preclinical, and clinical studies investigating the efficacy of kojic acid as a depigmenting agent for various forms of skin hyperpigmentation, including melasma, post-inflammatory hyperpigmentation, solar lentigines, and other pigmentary disorders.

The eligibility criteria were established before the literature search to ensure consistency during study selection. Studies were included if they met the following criteria: (1) published in English or Indonesian; (2) investigated the effects of kojic acid on skin hyperpigmentation; (3) employed clinical trials, laboratory experiments, in vivo animal studies, in vitro cell culture studies, or other experimental research designs; (4) reported measurable outcomes related to pigmentation changes, melanin production, tyrosinase activity, or clinical improvement of hyperpigmented lesions; and (5) were available in full-text format. Studies were excluded if they consisted of

review articles, editorials, commentaries, conference abstracts, opinion papers, or non-research publications. In addition, studies that did not specifically evaluate kojic acid, lacked relevant outcome measures, or had inaccessible full-text versions were excluded from the review. Establishing explicit inclusion and exclusion criteria is recommended to minimize selection bias and improve the methodological rigor of systematic reviews.

A comprehensive literature search was conducted using several international electronic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. These databases were selected because they provide extensive coverage of peer-reviewed publications in dermatology, pharmacology, cosmetic science, and biomedical research. The search strategy combined Medical Subject Headings (MeSH) terms with free-text keywords connected using Boolean operators (AND and OR). The principal search terms included *"kojic acid," "hyperpigmentation," "melasma," "post-inflammatory hyperpigmentation," "skin pigmentation," "depigmentation," "tyrosinase inhibition,"* and *"melanogenesis."* To maximize the retrieval of relevant studies, the reference lists of all eligible articles were manually examined to identify additional publications that were not captured during the electronic database search. This combination of electronic and manual searching is recommended to improve the completeness of systematic reviews.

The study selection process consisted of three sequential stages. First, duplicate records retrieved from different databases were identified and removed using reference management software. Second, titles and abstracts were screened independently according to the predefined eligibility criteria. Finally, full-text articles considered potentially relevant were evaluated in detail before inclusion in the final review. The study selection process followed the PRISMA 2020 flow diagram to ensure transparency throughout the review procedure.

Data were extracted using a standardized data extraction form to ensure consistency across all included studies. The extracted information comprised the first author's name, publication year, country of study, research design, sample characteristics, type of hyperpigmentation, kojic acid concentration, formulation, treatment duration, comparator intervention, primary outcome measures, reported efficacy, and adverse effects. The extracted data were subsequently summarized in tabular form to facilitate comparison of methodological characteristics and clinical outcomes among the included studies.

The methodological quality of the included studies was critically evaluated by considering the study design and potential sources of bias. The assessment focused

on key methodological domains, including randomization procedures, allocation concealment, blinding of participants and outcome assessors, sample size adequacy, completeness of outcome reporting, and consistency of statistical analyses. These criteria were adapted from recommendations provided in the Cochrane Handbook for Systematic Reviews of Interventions, which is widely recognized as the international standard for assessing the risk of bias in health research.

The findings were synthesized using a narrative synthesis approach because of the anticipated heterogeneity in study designs, participant characteristics, intervention protocols, outcome measures, and follow-up durations. Particular attention was given to identifying consistent patterns regarding the effectiveness of kojic acid, factors influencing therapeutic outcomes, safety profiles, and reported adverse events. Furthermore, comparisons were made according to kojic acid concentration, formulation type, treatment duration, and combination therapies to determine the clinical conditions under which kojic acid demonstrated the greatest depigmenting efficacy. This qualitative synthesis provides a comprehensive evidence-based overview of the current scientific knowledge regarding the role of kojic acid in the management of skin hyperpigmentation.

FINDINGS AND DISCUSSION

The findings of this systematic literature review indicate that kojic acid demonstrates consistent effectiveness in reducing skin hyperpigmentation across a wide range of experimental, preclinical, and clinical studies. Although the magnitude of therapeutic improvement varies depending on patient characteristics, skin phototype, concentration, formulation, treatment duration, and the underlying cause of pigmentation, the overall body of evidence supports kojic acid as one of the most effective naturally derived depigmenting agents currently used in dermatological and cosmetic practice. Most of the reviewed studies reported significant reductions in pigmentation intensity following regular topical application of kojic acid, particularly in patients with melasma, post-inflammatory hyperpigmentation (PIH), and solar-induced pigmentation. Clinical improvement generally became apparent after continuous treatment for approximately four to twelve weeks, although more persistent pigmentary disorders often required longer therapeutic periods to achieve optimal outcomes.

The effectiveness of kojic acid is primarily attributed to its ability to inhibit tyrosinase, the rate-limiting enzyme responsible for melanin biosynthesis (Peng et al., 2022). Kojic acid acts by chelating the copper ions located within the active site of tyrosinase, thereby preventing the enzymatic conversion of tyrosine into L-DOPA

and subsequently reducing melanin production. This mechanism directly interrupts melanogenesis and gradually decreases the accumulation of melanin within epidermal keratinocytes. Experimental investigations have consistently demonstrated that inhibition of tyrosinase results in a measurable decline in melanin synthesis without causing permanent destruction of melanocytes, making kojic acid a safer alternative to several older depigmenting agents. Beyond enzyme inhibition, recent molecular studies also suggest that kojic acid possesses antioxidant activity capable of reducing reactive oxygen species generated by ultraviolet radiation (Mawazi et al., 2026). Because oxidative stress stimulates melanogenesis through multiple intracellular signaling pathways, the antioxidant effect of kojic acid may further contribute to the reduction of hyperpigmentation, particularly in individuals exposed to chronic ultraviolet irradiation.

The reviewed literature further indicates that the therapeutic performance of kojic acid is substantially enhanced when administered in combination with other depigmenting agents. Combination formulations containing kojic acid together with hydroquinone, glycolic acid, arbutin, niacinamide, retinoids, vitamin C, or azelaic acid consistently produced greater reductions in pigmentation than kojic acid monotherapy (Hu et al., 2022). This finding reflects the multifactorial nature of melanogenesis, in which different active compounds target complementary biological pathways. Hydroquinone primarily suppresses melanin synthesis through direct inhibition of melanocyte metabolism, glycolic acid accelerates epidermal turnover and facilitates removal of pigmented keratinocytes, niacinamide inhibits melanosome transfer from melanocytes to keratinocytes, while antioxidants such as vitamin C reduce oxidative stress that promotes pigmentation. Consequently, combination therapy simultaneously interrupts several stages of pigment formation, producing faster and more sustained clinical improvement than single-agent treatment. Several randomized clinical trials have demonstrated that triple-combination formulations containing kojic acid achieve significantly greater reductions in melasma severity scores compared with formulations lacking kojic acid, further supporting its value as an adjunctive depigmenting ingredient.

Another important observation emerging from the reviewed literature concerns the influence of treatment duration and formulation characteristics on clinical efficacy. Studies consistently reported that prolonged application, usually extending beyond eight weeks, resulted in more pronounced reductions in pigmentation intensity. However, excessive treatment duration did not always produce proportional clinical benefits and occasionally increased the incidence of skin

irritation. Moreover, different pharmaceutical formulations demonstrated variable therapeutic performance despite containing similar concentrations of kojic acid (Saeedi et al., 2023). Creams, serums, gels, lotions, and nanoformulations exhibited differences in skin penetration, chemical stability, and patient compliance, all of which influenced clinical outcomes. Recent pharmaceutical research has therefore focused on improving delivery systems capable of enhancing skin permeation while minimizing degradation of the active compound. Encapsulation technologies, liposomal formulations, and nanocarrier systems have shown promising results by increasing formulation stability and maintaining prolonged release of kojic acid within the epidermis, thereby potentially improving depigmenting efficacy while reducing local irritation.

Despite its demonstrated effectiveness, the literature consistently identifies several limitations associated with kojic acid therapy, particularly regarding its safety profile. The most frequently reported adverse effects include erythema, burning sensation, pruritus, skin irritation, scaling, and allergic contact dermatitis. These reactions are generally mild to moderate in severity and tend to occur more frequently among individuals with sensitive skin, impaired skin barrier function, or prolonged exposure to higher concentrations of kojic acid (Bernauer et al., 2023). Importantly, most adverse reactions are reversible following treatment discontinuation or dose reduction. Compared with hydroquinone, kojic acid is generally considered to possess a more favorable long-term safety profile because it has not been consistently associated with exogenous ochronosis or permanent pigmentary complications. Nevertheless, clinicians should carefully individualize treatment regimens according to patient skin type, previous dermatological history, and treatment tolerance to minimize undesirable reactions.

One of the most frequently discussed issues in recent pharmaceutical literature concerns the chemical instability of kojic acid. The compound is susceptible to oxidation upon exposure to oxygen, light, elevated temperatures, and inappropriate pH conditions, resulting in discoloration and reduced biological activity during storage. This instability partially explains why commercial products containing similar concentrations of kojic acid may produce substantially different therapeutic outcomes. Formulation stability therefore represents a critical determinant of clinical effectiveness. Manufacturers increasingly combine kojic acid with antioxidants, stabilizing excipients, chelating agents, and optimized delivery vehicles to preserve chemical integrity throughout product storage and application. Advances in pharmaceutical formulation technology are expected to further improve the stability,

bioavailability, and therapeutic consistency of kojic acid-containing products in the future (Brtko, 2022).

The findings also demonstrate that therapeutic success is influenced by the underlying etiology of hyperpigmentation. Melasma, which is strongly associated with hormonal influences, ultraviolet exposure, and genetic susceptibility, often requires prolonged therapy and comprehensive photoprotection to prevent recurrence. In contrast, post-inflammatory hyperpigmentation resulting from acne, eczema, or dermatological procedures frequently responds more rapidly to kojic acid therapy because pigmentation gradually diminishes as inflammation subsides. Consequently, treatment effectiveness should not be evaluated solely according to the active ingredient but also in relation to disease pathogenesis, patient adherence, sun protection practices, and concomitant skincare routines. Daily sunscreen application remains an essential component of successful depigmentation therapy because continued ultraviolet exposure stimulates melanogenesis and may counteract the therapeutic effects of topical depigmenting agents.

Although the available evidence strongly supports the efficacy of kojic acid, several limitations within the existing literature should be acknowledged. Considerable heterogeneity exists regarding study design, sample size, participant ethnicity, skin phototype, treatment duration, kojic acid concentration, outcome measurement methods, and comparator interventions. These methodological differences complicate direct comparisons across studies and limit the ability to establish universally applicable treatment recommendations. Furthermore, relatively few studies have evaluated the long-term efficacy and safety of kojic acid beyond six months of continuous use. Additional well-designed multicenter randomized controlled trials involving diverse populations and standardized outcome measures are therefore required to determine the optimal concentration, formulation, treatment duration, and combination strategies that maximize therapeutic benefits while minimizing adverse reactions.

The evidence synthesized in this review supports the conclusion that kojic acid is an effective topical depigmenting agent for managing various forms of skin hyperpigmentation. Its principal therapeutic mechanism involves inhibition of tyrosinase activity, accompanied by antioxidant properties that further suppress melanogenesis. The greatest clinical benefits appear to be achieved when kojic acid is incorporated into stable pharmaceutical formulations and combined with complementary depigmenting agents targeting multiple pathways involved in pigment formation. Nevertheless, treatment outcomes remain dependent on

formulation quality, patient adherence, disease characteristics, and appropriate photoprotection. Consequently, kojic acid should be regarded as an evidence-based therapeutic option for hyperpigmentation that offers favorable efficacy and acceptable safety when appropriately formulated and clinically monitored, while continued pharmaceutical innovation and high-quality clinical research remain necessary to optimize its long-term therapeutic potential.

CONCLUSION

This systematic literature review demonstrates that kojic acid is an effective topical depigmenting agent for the management of various forms of skin hyperpigmentation, including melasma, post-inflammatory hyperpigmentation, solar lentigines, and other pigmentary disorders. The available evidence consistently indicates that its primary mechanism of action involves the inhibition of tyrosinase, the key enzyme responsible for melanin biosynthesis, resulting in reduced melanin production and gradual improvement of hyperpigmented lesions. In addition to its anti-tyrosinase activity, kojic acid possesses antioxidant properties that may further suppress melanogenesis by reducing oxidative stress induced by ultraviolet radiation. These complementary mechanisms contribute to its therapeutic effectiveness and support its continued use in dermatological and cosmetic formulations.

The findings further suggest that the clinical efficacy of kojic acid is influenced by several factors, including treatment duration, formulation stability, concentration, patient characteristics, and the underlying cause of hyperpigmentation. Greater therapeutic improvement is generally observed after continuous application for several weeks, while combination therapy with agents such as hydroquinone, glycolic acid, niacinamide, arbutin, or vitamin C frequently produces superior outcomes compared with kojic acid monotherapy. Such combination strategies target multiple pathways involved in melanogenesis and epidermal renewal, thereby enhancing depigmenting efficacy and accelerating clinical improvement.

Despite these favorable outcomes, the review also highlights several limitations associated with kojic acid therapy. Mild adverse reactions, including erythema, skin irritation, burning sensation, and contact dermatitis, remain the most commonly reported side effects, particularly among individuals with sensitive skin or following prolonged use of high-concentration formulations. Furthermore, the chemical instability of kojic acid represents an important challenge because oxidation during storage may reduce its biological activity and contribute to variability in therapeutic responses among commercially available products.

The current body of evidence supports kojic acid as a safe and effective treatment option for skin hyperpigmentation when appropriately formulated and used under suitable clinical conditions. Nevertheless, considerable heterogeneity among existing studies including differences in study design, formulation type, treatment protocols, outcome measures, and follow-up duration limits direct comparison of findings. Future research should prioritize large-scale, multicenter randomized controlled trials with standardized methodologies to establish the optimal concentration, formulation, treatment duration, and combination regimens. In addition, advances in pharmaceutical formulation technology aimed at improving the stability, bioavailability, and skin penetration of kojic acid are expected to further enhance its therapeutic potential. Such investigations will strengthen the evidence base and contribute to the development of more effective, safer, and evidence-based depigmenting therapies for patients with hyperpigmentation disorders.

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