Ad-Dawaa' Journal of Pharmaceutical Sciences
ISSN: 2654-7392, E-ISSN: 2654-6973
Vol. 8, No. 2, December 2025, p. 157-174
DOI: https://doi.org/10.24252/djps.v8i2.57608

A Comprehensive Review of Kojic Acid Dipalmitate: Advanced Skin Brightening Technology in Contemporary Cosmetics

Alifia Ramadhanty Prameswari*, Anis Yohana Chaerunnisaa, Patihul Husni

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang 45363, West Java, Indonesia

Article history:
Submited: 09-06-2025
Revised: 06-08-2025
Accepted: 30-08-2025

Corresponding author e-mail: alifia24007@mail.unpad.ac.id

Cite this article: Prameswari, A. R., Chaerunnisaa, A. Y., Husni, P. (2025) A Comprehensive Review of Kojic Acid Dipalmitate: Advanced Skin Brightening Technology in Contemporary Cosmetics. Ad-Dawaa' J. Pharm. Sci. 8(2): 157-174 .

ABSTRACT

Introduction: *Hyperpigmentation disorders represent a significant concern in dermatology and cosmetic science, with traditional treatments often limited by stability issues, irritation potential, and suboptimal efficacy. Kojic Acid Dipalmitate (KAD), a lipophilic derivative of kojic acid, has emerged as a promising alternative in advanced skin brightening formulations due to its enhanced physicochemical properties and improved safety profile.* ***Aims***: *This review aimed to evaluate the stability considerations, optimal concentration ranges, delivery system technologies, and clinical efficacy of KAD in topical applications for hyperpigmentation management.* ***Methods***: *A comprehensive analysis of recent literature was conducted, examining in vitro studies assessing tyrosinase inhibition and stability profiles, ex vivo investigations of skin penetration and retention, and in vivo clinical evaluations of efficacy and safety. Particular attention was directed toward advanced delivery systems including solid lipid nanoparticles, nanoemulsions, and ethosomal formulations.* ***Results***: *KAD demonstrates superior stability against oxidation, pH fluctuations, and thermal stress compared to conventional kojic acid. Optimal formulations contain 1-5% KAD, with sophisticated delivery systems achieving comparable efficacy at lower concentrations (0.1-0.2%) due to enhanced bioavailability. Solid lipid nanoparticles (70 nm) exhibited controlled release kinetics with 80% KAD released over 24 hours, while nanoemulsions (<130 nm) showed >95% stability for 30 days under refrigeration. Clinical evaluations confirmed 40-50% reduction in melanin indices with minimal irritation, along with improved skin hydration and elasticity. KAD also demonstrated antimicrobial activity against Staphylococcus aureus and antioxidant capacity comparable to 1 mM ascorbic acid.* ***Conclusion***: *KAD represents a significant advancement in depigmentation technology, successfully balancing efficacy and tolerability through enhanced stability and targeted delivery. Its integration into sophisticated vehicle systems optimizes performance while minimizing adverse effects, positioning KAD as an exemplary ingredient for next-generation skin brightening formulations in contemporary cosmeceuticals.*

KEYWORDS: *Kojic acid dipalmitate, kojic acid derviates, cosmetics, depigmenting agent, skin brightening.*

INTRODUCTION

Hyperpigmentation disorders represent a significant dermatological concern affecting an estimated 15-35% of the global population, with notably higher prevalence among individuals with darker skin phototypes (Davis & Callender, 2010; Silpa-archa et al., 2017). These conditions, characterized by irregular darkening of the skin, manifest as melasma, post-inflammatory hyperpigmentation, solar lentigines, and other pigmentary abnormalities that can significantly impact patients' quality of life and psychological well-being. The pathophysiology primarily involves dysregulation of melanogenesis, the biological process of melanin production within melanocytes, triggered by various factors including ultraviolet radiation, hormonal fluctuations, inflammatory responses, and genetic predisposition (Sarkar et al., 2013).

The quest for effective skin brightening solutions has a long and complex history in the cosmetic and pharmaceutical industries. Traditional depigmenting agents such as hydroquinone, introduced in the 1960s, have served as the gold standard for decades despite concerns regarding long-term safety, including ochronosis and potential carcinogenicity with prolonged use (Desai, 2014). Mercury compounds, once widely utilized, have been globally banned due to their established toxicity. Corticosteroids, while effective for certain inflammatory pigmentary disorders, carry significant risks with extended application. This historical context has created a compelling imperative for the development of safer alternatives that maintain efficacy while minimizing adverse effects (Gillbro & Olsson, 2011a).

Market analysis indicates substantial and growing consumer demand for skin brightening products, with the global market valued at approximately $11.62 billion in 2024 and projected to reach $18.91 billion by 2033, reflecting a compound annual growth rate of 6.7% (Bothare, 2024). This expansion is driven by increasing consumer awareness of hyperpigmentation treatments, growing aesthetic concerns across diverse demographic groups, and the rising incidence of pigmentary disorders associated with environmental factors and aging populations. Significantly, consumer preferences have shifted decisively toward products perceived as "natural," "clean," and demonstrably safe for long-term use, creating strong market incentives for innovation in this sector (Castilla-Miguel & Aramendia-Muneta, 2023).

Within this evolving landscape, kojic acid derivatives have emerged as promising candidates for advanced skin brightening formulations. Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one), initially

identified as a fungal metabolite from Aspergillus and Penicillium species, has established efficacy as a tyrosinase inhibitor, thereby interrupting the critical rate-limiting step in melanin synthesis (Burnett et al., 2010). However, conventional kojic acid presents significant formulation challenges, including stability issues and limited penetration capacity. These limitations have catalyzed the development of derivatives such as kojic acid dipalmitate (KAD)—a diester formed by esterification of kojic acid with palmitic acid—which demonstrates enhanced stability, improved lipophilicity for transdermal delivery, and potentially superior efficacy profiles (Ayuhastuti et al., 2024).

This comprehensive review aims to critically evaluate the current scientific understanding of kojic acid dipalmitate as an advanced skin brightening technology in modern cosmeceutical applications. Specifically, we will examine its chemical structure and properties, mechanisms of action in melanogenesis inhibition, clinical efficacy compared to conventional agents, safety and toxicological profiles and formulation considerations for optimized delivery. Additionally, this review will identify research gaps and future directions in the development of kojic acid dipalmitate-based formulations. By synthesizing evidence from peer-reviewed literature, clinical studies, patent analyses, and market data, this review seeks to provide dermatologists, cosmetic scientists, formulators, and regulatory professionals with an authoritative resource for informed decision-making regarding this promising skin brightening technology.

MOLECULAR PROPERTIES AND STRUCTURES

Kojic acid dipalmitate (KAD) represents a significant advancement in skin brightening technology through the strategic modification of its parent compound. Chemically defined as 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one dipalmitate, KAD is synthesized via esterification of kojic acid with two molecules of palmitic acid at the hydroxyl groups located at positions 5 and 7 of the pyrone ring, as illustrated in Figure 1 (Gonçalez et al., 2015).

The incorporation of two long-chain fatty acid residues fundamentally transforms the physicochemical profile of the resulting compound. Perhaps most notably, KAD exhibits remarkable stability under various environmental conditions that typically compromise the efficacy of conventional kojic acid. Experimental studies have demonstrated that KAD maintains structural integrity at pH values ranging from 3.5 to 8.0, showing less than 5% degradation after 30 dyas of storage at room temperature (Mohammadi et al., 2021

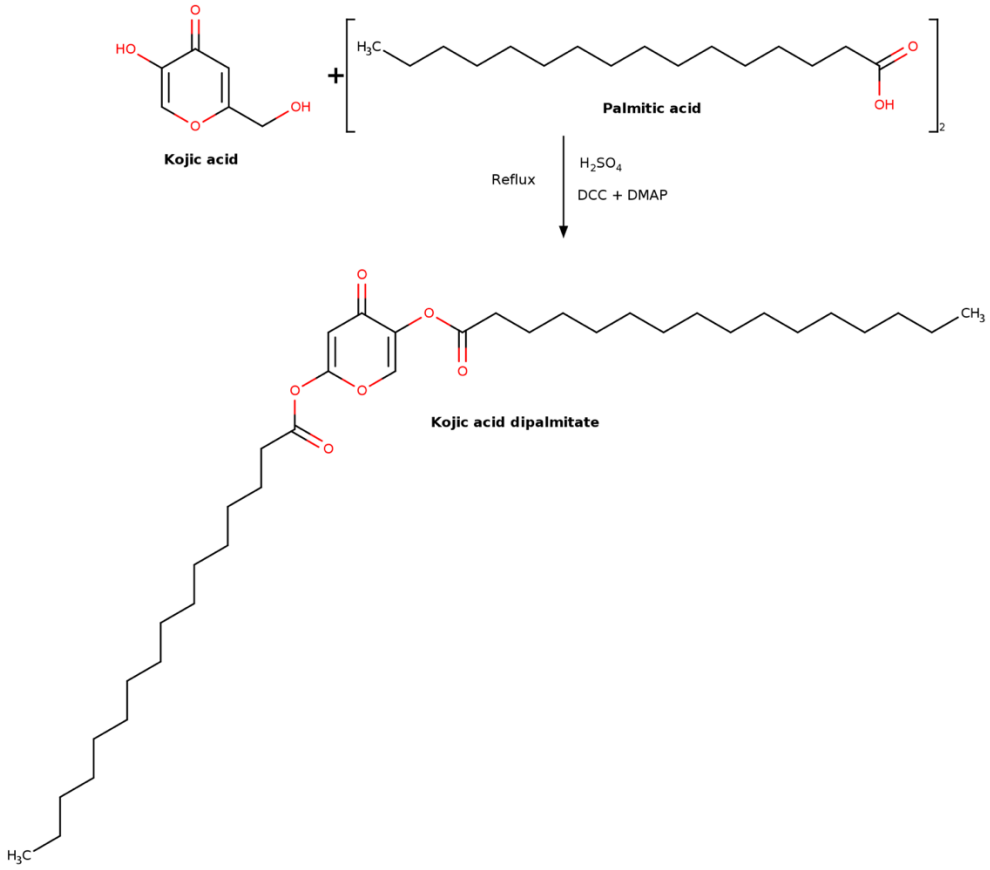

Figure 1. Schematic illustration of kojic acid dipalmitate synthesis via esterification of kojic acid with palimitic acid

Zilles et al., 2023). This enhanced stability is attributed to the protective effect of the palmitate chains, which shield the reactive hydroxyl groups responsible for the oxidative vulnerability of the parent compound.

Spectroscopic analyses confirm that KAD retains the essential pyrone ring structure responsible for tyrosinase inhibition while gaining significantly improved resistance to photodegradation. Under accelerated stability testing conditions with UV exposure, KAD exhibited less degradation compared to unmodified kojic acid under identical conditions (Ayuhastuti et al., 2024). This photostability represents a critical advancement for formulation scientists, as it eliminates the need for extensive protective packaging and specialized storage conditions that have historically complicated the commercialization of kojic acid-based products.

The lipophilic nature of KAD, quantified by its octanol-water partition coefficient (log P) of approximately 8.7 compared to kojic acid's -0.64, dramatically influences its solubility profile and formulation compatibility (Gonçalez et al., 2015; Tazesh et al., 2022a). This heightened lipophilicity enables ready incorporation into oil-based delivery systems, emulsions, and lipid nanoparticles—versatility that expands the rang of cosmetic formulations capable of

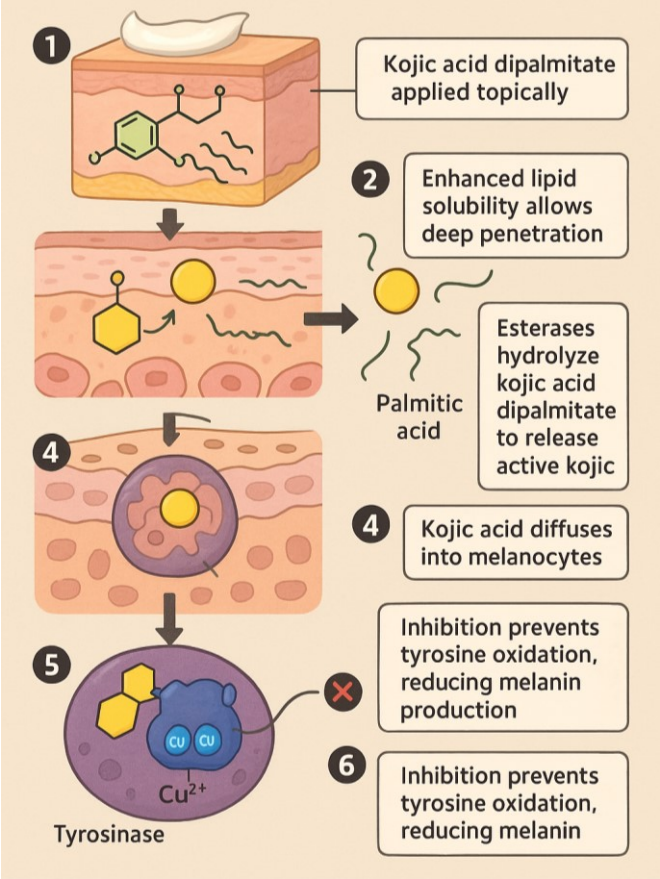

Figure 2. Tyrosinase inhibition pathway of kojic acid dipalmitate (Chen et al., 2019)

effectively delivering this active ingredient. Additionally, the lipophilic character contributes to enhanced skin permeation through improved compatibility with the stratum corneum, potentially facilitating more effective delivery to melanocytes located at the basal layer of the epidermis.

MECHANISMS OF ACTION

Tyrosinase Inhibition Pathway

KAD exerts its depigmenting effects through a sophisticated biochemical cascade that ultimately results in the reduction of melanin synthesis in epidermal melanocytes. The primary mechanism centers on tyrosinase inhibition, albeit through a unique prodrug approach that distinguishes KAD from conventional depigmenting agents. Upon topical application, KAD must first undergo enzymatic biotransformation via cutaneous esterases present within the skin's upper layers, as presented in Figure 2 (Chen et al., 2019; Lajis et al., 2012). This hydrolytic process cleaves the palmitate chains, liberating kojic acid within the target tissue—a conversion documented to occur at clinically relevant rates within 2-4 hours of application, with approximately 40-65% conversion efficiency depending on formulation characteristics and skin condition (M. Lee et al., 2020).

The released kojic acid then engages with tyrosinase—the rate-limiting copper-

containing metalloenzyme essential for melanogenesis—through a competitive inhibition mechanism. X-ray crystallography and molecular docking studies have elucidated the precise binding interactions, demonstrating that the hydroxyl groups at positions 5 and 7 of the kojic acid molecule form coordination bonds with the copper ions at the tyrosinase active site (Pillaiyar et al., 2015). This chelation effectively prevents the binding of natural substrates such as tyrosine and 3,4-dihydroxyphenylalanine (DOPA), thereby inhibiting the critical oxidative reactions necessary for melanin production with an IC_{50} value of approximately 3.63 μM in cell-free enzyme assays (Y. S. Lee et al., 2006)

The enzymatic hydrolysis requirement for KAD creates a controlled-release effect that may offer several pharmacokinetic advantages over direct application of kojic acid. At the molecular level, the inhibition of tyrosinase disrupts the conversion of tyrosine to DOPA and subsequently to dopaquinone—the initial and rate-limiting steps in melanin biosynthesis. Importantly, the timing of this intervention is crucial, as it occurs at the earliest stage of the melanogenic pathway, preventing the formation of melanin precursors rather than addressing existing pigmentation. Consequently, clinical outcomes typically manifest gradually over several weeks as melanin turnover proceeds, with studies demonstrating measurable reductions in melanin content after 4-6 weeks of consistent application (Boo, 2019; Gillbro & Olsson, 2011b; Zolghadri et al., 2019).

Secondary Depigmentation Mechanisms

While tyrosinase inhibition represents the primary mode of action for kojic acid dipalmitate, emerging research has identified several secondary mechanisms that likely contribute to its overall depigmenting efficacy (see Figure 3). These complementary pathways may explain the enhanced clinical outcomes observed in comparative studies between KAD and single-mechanism depigmenting agents.

Significant among these secondary mechanisms is KAD's demonstrated interference with melanosome transfer—the critical process by which melanin-containing organelles are transported from melanocytes to surrounding keratinocytes. In vitro co-culture systems utilizing fluorescently labeled melanosomes have revealed that KAD treatment (100 μM) reduces melanosome transfer efficiency by approximately 77 – 79% compared to untreated controls (Moharir et al., 2024). The molecular basis for this effect appears to involve disruption of the dendrite formation in melanocytes and alteration of the protease-activated receptor-2 (PAR-2) signaling pathway that mediates phagocytosis of melanosomes by of melanosomes by keratinocytes (Kim et al.,

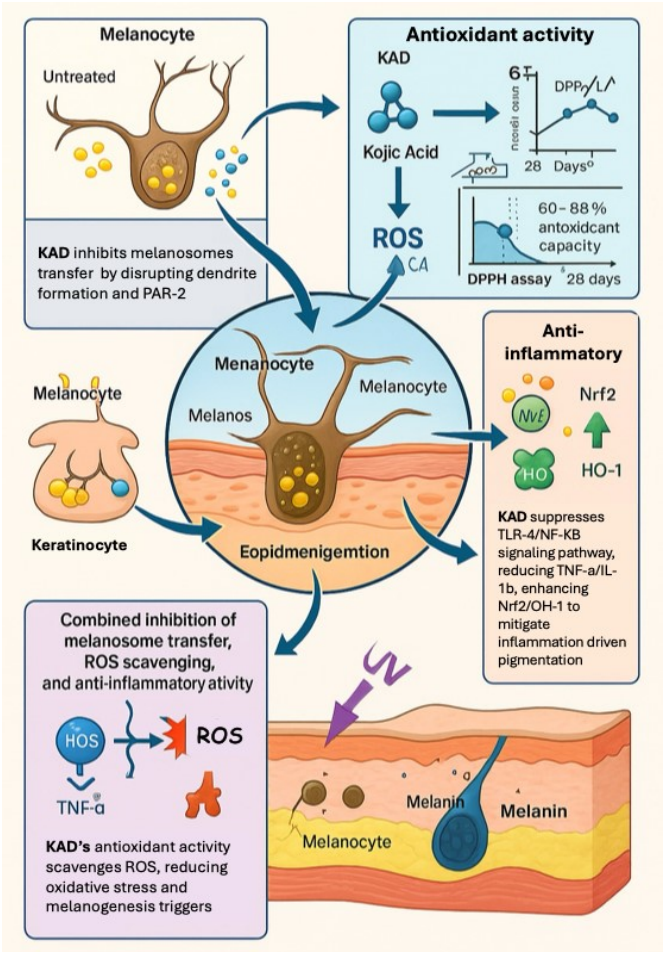

Figure 3. Multifaceted depigmenting mechanism of kojic acid dipalmitate

2010). This melanosome transfer inhibition provides a secondary intervention point that may enhance the overall depigmenting effect beyond what could be achieved through tyrosinase inhibition alone.

Antioxidant activity represents another important secondary mechanism attributed to KAD. Following conversion to kojic acid within the skin, potent free radical scavenging capabilities become evident, with particular efficiency against reactive oxygen species (ROS) such as superoxide anions and hydroxyl radicals. This antioxidant activity has been quantified using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays, demonstrating approximately 60-65% of the antioxidant capacity over 28 days ((Gonçalez et al., 2015). Given that oxidative stress is a well-established trigger for melanogenesis through multiple pathways—including direct tyrosinase activation and upregulation of microphthalmia-associated transcription factor (MITF)—this antioxidant effect may provide additional protection against UV-induced pigmentation and contribute to the overall skin brightening outcome (Nahhas et al., 2019).

Anti-inflammatory properties further contribute to KAD's depigmenting potential, particularly for post- inflam

matory hyperpigmentation. Research on kojic acid, a compound closely related to kojic dipalmitate, demonstrates significant anti-inflammatory effects, particularly in the context of neuroinflammation. Kojic acid has been shown to suppress inflammation induced by lipopolysaccharides (LPS) by downregulating key inflammatory signaling pathways, such as the TLR4/NF-κB pathway. This downregulation leads to reduced expression of pro-inflammatory proteins and cytokines, including TNF-α and IL-1β, in the brain. Additionally, kojic acid increases the expression of antioxidant proteins like Nrf2 and HO-1, which further helps to counteract oxidative stress associated with inflammation (Ali et al., 2024). While direct studies on kojic dipalmitate's anti-inflammatory properties are limited, its structural similarity to kojic acid suggests it may share similar biological activities. Since these inflammatory mediators can directly stimulate melanogenesis through various pathways, including the activation of prostaglandin E2 production and subsequent enhancement of tyrosinase activity, the anti-inflammatory effect of KAD provides an additional mechanism for preventing or mitigating hyperpigmentation development.

The multifaceted mechanisms of KAD—encompassing direct tyrosinase inhibition, interference with melanosome transfer, antioxidant protection, and anti-inflammatory effects—collectively contribute to its clinical efficacy as a skin brightening agent. This mechanistic diversity not only enhances its depigmenting potential but may also provide advantages for addressing the complex and multifactorial nature of hyperpigmentation disorders in diverse patient populations.

EFFİCACY PROFİLE

The efficacy of KAD as a skin brightening agent has been substantiated through a progressive body of scientific evidence, beginning with foundational in vitro studies and culminating in rigorous clinical investigations (Table 1). Initial assessments of KAD's potential were conducted in melanocyte monoculture systems, where treatment with KAD demonstrated inhibition of melanin synthesis. Quantitative analysis revealed that KAD at 1 – 18.6 μM reduced melanin production by 62-68% compared to untreated controls, with minimal cytotoxicity observed even at the highest tested concentrations (Gonçalez et al., 2015; Tanveer et al., 2022). These findings established a favorable therapeutic index that distinguished KAD from certain conventional brightening agents known for their narrow safety margins.

In vitro research confirms that KAD exhibits potent tyrosinase inhibitory activi-

Table 1. Evidence of kojic acid dipalmitate (KAD) for hyperpigmentation

Evidence	Mechanism/Effect	Key Findings	References
In Vitro Studies	Tyrosinase inhibition	KAD hydrolyzes to release kojic acid, which chelates copper ions in tyrosinase, blocking melanin synthesis. Nanoemulsions enhance epidermal permeation	Tanveer et al., 2022
	Antioxidant activity	KAD exhibits free radical scavenging properties, reducing oxidative stress that triggers melanogenesis	Lajis et al., 2012; Tazesh et al., 2022b
	Melanosome Transport Disruption	KAD downregulates Rab27a and melanophilin, proteins critical for melanosome transfer	Lajis et al., 2012
	Cytotoxicity & Safety	KAD esters show lower cytotoxicity compared to kojic acid in B16F1 melanoma cells	Lajis et al., 2012; Syed Azhar et al., 2020
Clinical Evidence	Cosmetic Formulations	Over 132 commercial products (creams, serums) use KAD (up to 3%) for skin-lightening, with reported efficacy	Lajis et al., 2012
	Ethosomal Gel Efficacy	KAD-loaded ethosomal gel reduces melanin, erythema, and sebum levels while improving skin hydration	Tanveer et al., 2022
	Synergistic Formulations	KAD combined with azelaic acid, glycolic acid, and niacinamide enhances depigmenting effects	Gautam, 2023
	Safety Profile	KAD formulations show reduced irritation compared to kojic acid, attributed to improved stability	Ayuhastuti et al., 2024; Lajis et al., 2012

ty comparable to kojic acid itself. Experimental assays have demonstrated that KAD-loaded nanoemulsions can reduce melanin synthesis by up to 50%, while simultaneously providing antioxidant activity equivalent to 1 mM ascorbic acid (Zilles et al., 2023). Additional studies focusing on ethosomal formulations have reported high entrapment efficiency of approximately 90% alongside sustained release kinetics that conform to the Korsmeyer–Peppas model with an impressive correlation coefficient of R^2 = 0.9964 (Syed Azhar et al., 2020). When examining stability and release kinetics, solid lipid nanoparticles (SLNs) loaded with KAD have exhibited prolonged release profiles, achieving 80% release over a 24-hour period, which represents a significant improvement compared to the rapid release observed with non-encapsulated KAD (Mohammadi et al., 2021). Furthermore, nanoemulsions have maintained greater than 95% KAD incorporation efficiency and stability for 30 days under refrigeration conditions, highlighting their particular suitability for topical applications (Zilles et al., 2023).

Beyond its primary depigmentation role, KAD-based nanoemulsions have demonstrated notable antimicrobial activity against Staphylococcus aureus, producing an inhibition zone of 8.0 mm, which surpasses the performance of free kojic acid esters that achieved inhibition zones of only 6.5 mm (Syed Azhar et al., 2020).

Ex vivo Franz cell experiments have revealed that KAD-loaded nano-creams penetrate the stratum corneum effectively, with drug release patterns comparable to conventional creams. However, a significant advantage emerges in retention capabilities, as nano-creams have been shown to retain KAD in hair follicles for more than seven days, compared to less than three days for standard creams, a benefit attributed to nanoparticle entrapment (Al-Edresi & Saringat, 2010). SLN-based formulations have achieved maximum epidermal concentration, effectively targeting melanocytes in the viable epidermis, as conclusively demonstrated in ex vivo skin models (Mohammadi et al., 2021). In vivo studies using animal models have shown that ethosomal gels loaded with KAD reduced melanin and erythema levels in Wistar rats by 40–50%, while simultaneously improving skin hydration and elasticity parameters (Tanveer et al., 2022). Zebrafish toxicity studies have indicated low toxicity profiles with an LC_{50} exceeding 500 µg/mL, and normal embryonic development at concentrations equal to or below 250 µg/mL, thereby affirming the safety profile for topical application (Syed Azhar et al., 2020). Human clinical evaluations of KAD ethosomal gel have demonstrated significant reductions in melanin index and sebum levels, accompanied by measurable improvements in skin hydration among volunteer participants (Tanveer et al., 2022). When compared to alternative depigmenting agents, KAD demonstrates superior performance over hydroquinone and arbutin in terms of safety, exhibiting minimal irritation and cytotoxicity (Ayuhastuti et al., 2024; Saeedi et al., 2019). Its inherent lipophilic nature enhances compatibility with lipid-based delivery systems such as SLNs and nanoemulsions, thereby improving bioavailability compared to the more hydrophilic kojic acid formulations currently available.

FORMULATION SCIENCE OF KOJIC ACID DIPALMITATE

Optimal Concentration and Delivery Systems

Kojic acid dipalmitate (KAD) has established itself as a prominent depigmenting agent in modern cosmeceuticals, primarily due to its enhanced stability, reduced irritation potential, and targeted melanogenesis inhi-

bition properties. The therapeutic efficacy of KAD in topical formulations is significantly influenced by both its concentration and the delivery system employed, factors that collectively determine its bioavailability, skin penetration capabilities, and ultimate therapeutic outcomes.

The optimal concentration range for KAD in topical formulations typically spans between 1% and 5%, with the specific concentration dependent upon the formulation type and intended clinical application. Research indicates that concentrations exceeding 5% do not significantly enhance efficacy but may increase the risk of crystallization in water-based products, thereby reducing bioavailability. Oil-based creams containing 3–5% KAD demonstrate superior whitening effects, attributable to the compound's inherent lipid solubility, which facilitates deeper epidermal penetration and sustained release characteristics (Qun & Jing, 2008). In contrast, advanced delivery systems such as nanoemulsions and solid lipid nanoparticles (SLNs) achieve comparable depigmentation results at substantially lower concentrations, typically 1–2 mg/mL (equivalent to 0.1–0.2%). This enhanced efficiency stems from their superior encapsulation efficiency exceeding 95% and nanoscale droplet sizes below 130 nm, both of which optimize melanocyte targeting. These sophisticated systems effectively mitigate the need for higher concentrations by significantly improving drug retention within the stratum corneum and hair follicles, as evidenced by ex vivo studies demonstrating prolonged epidermal deposition (Mohammadi et al., 2021; Zilles et al., 2023).

The selection of an appropriate delivery system critically impacts KAD's stability profile, penetration capabilities, and overall therapeutic performance. Solid Lipid Nanoparticles, composed of biocompatible lipids such as glycerol monostearate, have proven particularly effective for KAD delivery. These systems exhibit high drug-loading capacity with particle sizes approximating 70 nm and controlled release kinetics, with 80% of KAD released over a 24-hour period. SLN-based cream formulations achieve maximal epidermal concentration, ensuring targeted delivery to melanocytes while simultaneously minimizing transepidermal water loss, a common limitation associated with conventional cream formulations (Mohammadi et al., 2021). This delivery platform also enhances photostability, effectively addressing the degradation challenges typically encountered with free kojic acid upon UV exposure (Ayuhastuti et al., 2024).

Nanoemulsions, especially those incorporating synergistic ingredients such

as rosehip oil, demonstrate remarkable clinical efficacy. Research incorporating 1 mg/mL KAD and 5% rosehip oil has documented droplet sizes below 130 nm, zeta potentials of −10 mV, and antioxidant activity comparable to 1 mM ascorbic acid. The lipophilic core structure of nanoemulsions facilitates efficient KAD solubilization, while their characteristically small droplet size increases surface area contacts with the stratum corneum, thereby enhancing permeation. Furthermore, refrigerated nanoemulsions maintain stability exceeding 95% for up to 30 days, rendering them suitable for long-term therapeutic applications (Zilles et al., 2023). Alternative delivery systems such as ethosomal gels, which combine ethanol and phospholipids, enhance skin hydration and elasticity parameters while reducing melanin production by 40–50% in vivo. Multiple emulsions (W/O/W) also demonstrate considerable promise, with droplet sizes approximating 1 μm and Newtonian flow behavior, ensuring uniform KAD distribution and reduced irritation potential compared to non-encapsulated formulations (Gonçalez et al., 2015). Combining KAD with complementary ingredients such as antioxidants (e.g., ascorbic acid) or specialized oils (e.g., rosehip oil) significantly amplifies its depigmenting effects. For example, the linoleic acid content in rosehip oil enhances skin regeneration processes, while its inherent antioxidant properties complement KAD's tyrosinase inhibition mechanism, collectively yielding approximately 50% reduction in melanin indices during clinical evaluations (Ghasemiyeh et al., 2024; Zilles et al., 2023). Such strategic combinations permit the use of lower KAD concentrations without compromising therapeutic efficacy, aligning with contemporary trends toward multifunctional, low-irritancy skincare formulations.

While KAD demonstrates superior safety compared to kojic acid, exhibiting minimal cytotoxicity with LC_{50} values exceeding 500 μg/mL in zebrafish models, prolonged application at high concentrations (>5%) may still present certain risks, including contact dermatitis. Advanced nano-delivery systems effectively mitigate these risks by reducing direct exposure to free KAD, as evidenced in both SLN and nanoemulsion studies where cell viability remained above 90% at 1% concentrations.

Stability Considerations and Vehicle Technology

The stability of kojic acid dipalmitate in cosmetic formulations represents a significant advantage over its parent compound but still requires careful consideration during product development. While KAD demonstrates substantially im-

proved resistance to oxidation and discoloration compared to unmodified kojic acid, its stability remains influenced by various formulation factors including pH, temperature, light exposure, and the presence of incompatible ingredients. Understanding these parameters is essential for developing commercial products with acceptable shelf-life and maintained efficacy throughout the usage period.

KAD demonstrates superior stability compared to kojic acid due to esterification, which protects its hydroxyl groups from oxidation and degradation under heat, light, and alkaline conditions 49. For instance, kojic acid degrades rapidly in oxidative environments, turning yellowish, whereas KAD retains structural integrity across a pH range of 3–10 and exhibits minimal color changes. Despite these advantages, KAD remains susceptible to oxidative stress in aqueous formulations. Studies reveal that liquid oxidative stress induced by hydrogen peroxide accelerates KAD degradation, with first-order kinetics dominating the reaction process. To mitigate this, formulations often incorporate antioxidants (e.g., ascorbic acid) or encapsulate KAD within oil-in-water (O/W) emulsions to shield it from reactive oxygen species. Temperature and pH also influence stability. KAD's melting point (97.8°C) ensures thermal resilience during manufacturing, but prolonged exposure to high temperatures (>60°C) during emulsification can degrade its efficacy. Additionally, while KAD is stable in alkaline environments, its solubility in oil-based systems necessitates careful pH balancing (5.0–8.0) to prevent crystallization in water-based formulations (Sainakham et al., 2024; Tazesh et al., 2022b).

The selection of appropriate delivery systems profoundly impacts KAD's stability profile, dermal penetration capabilities, and ultimate bioavailability. Solid Lipid Nanoparticles (SLNs), composed of biocompatible lipid components such as glycerol monostearate, have proven exceptionally effective for KAD delivery applications. These sophisticated nanoparticulate systems significantly enhance drug-loading capacity, typically achieving particle sizes approximating 70 nanometers, while simultaneously prolonging release kinetics with approximately 80% of encapsulated KAD released over a 24-hour duration. Additionally, SLNs substantially improve photostability by providing a protective shield against UV-induced degradation processes and ensure targeted delivery to melanocytes within the epidermal layer, as convincingly demonstrated through ex vivo skin model investigations. Moreover, SLN-based cream formulations effectively minimize transepidermal water loss, there-

by enhancing skin hydration parameters and reducing irritation potential (Ayuhastuti et al., 2024; Mohammadi et al., 2021).

Nanoemulsions, particularly those incorporating KAD with synergistic therapeutic agents such as rosehip oil, optimize both stability and penetration efficiency. These advanced systems consistently achieve droplet sizes below 130 nanometers, ensuring expansive surface area contact with the stratum corneum. For example, specialized formulations containing 1 mg/mL KAD combined with 5% rosehip oil have demonstrated antioxidant activity comparable to 1 mM ascorbic acid while maintaining stability exceeding 95% for periods up to 30 days under refrigerated storage conditions. To prevent crystallization phenomena, current formulation protocols recommend pre-dissolving KAD in appropriate oils such as isopropyl palmitate at 80°C prior to emulsification procedures. Alternative delivery platforms such as ethosomal gels, which ingeniously integrate ethanol and phospholipid components, enhance skin hydration characteristics while achieving melanin reduction of 40–50% in vivo. Multiple emulsion systems (W/O/W) with characteristic droplet sizes approximating 1 micrometer significantly improve KAD solubility across both hydrophilic and lipophilic phases, ensuring uniform distribution and diminished irritation potential. These sophisticated systems additionally facilitate co-encapsulation of complementary antioxidants, further stabilizing KAD during extended storage periods (Ayuhastuti et al., 2024; Sainakham et al., 2024).

CONCLUSION

KAD represents a significant advancement in depigmentation technology, addressing many limitations of conventional kojic acid through enhanced stability, improved safety profiles, and favorable clinical outcomes. The integration of KAD into sophisticated delivery systems, notably solid lipid nanoparticles, nanoemulsions, and ethosomal formulations, substantially enhances its bioavailability and targeted delivery to melanocytes while minimizing irritation potential across diverse skin types. Formulations containing 1-5% KAD demonstrate optimal efficacy without increasing adverse effects, particularly when combined with complementary ingredients such as antioxidants and specialized botanical oils. KAD's remarkable resistance to oxidation, pH fluctuations, and thermal stress suggests potential as a commercially viable alternative to traditional brightening agents, with encapsulation technologies

further extending its stability throughout the product lifecycle.

Clinical evidence supports KAD's effectiveness in melanin reduction and skin hydration improvement with minimal irritation, while its additional antimicrobial and antioxidant properties provide value beyond depigmentation alone. However, several research gaps warrant attention. Long-term clinical validation, studies across more diverse populations, and direct comparative trials with established brightening agents are needed to fully characterize KAD's therapeutic profile. Future investigations should also explore KAD's synergistic potential when combined with other cosmeceutical agents and evaluate its real-world efficacy across varied environmental conditions. As the cosmeceutical industry increasingly demands evidence-based formulations with enhanced safety profiles, KAD positions itself as a promising candidate that may successfully balance efficacy and tolerability in addressing one of dermatology's most persistent challenges.

REFERENCES

Al-Edresi, S., & Saringat, H. (2010). In-vitro and in-vivo evaluation of a photo-protective kojic dipalmitate loaded into nano-creams. Asian Journal of Pharmaceutical Sciences, 5, 251–265.

Ali, W., Choe, K., Park, J. S., Ahmad, R., Park, H., Kang, M. H., Park, T., & Kim, M.-O. (2024). Kojic acid reverses LPS-induced neuroinflammation and cognitive impairment by regulating the TLR4/NF-κB signaling pathway. Frontiers in Pharmacology, 15. https://doi.org/10.3389/fphar.2024.1443552

Ayuhastuti, A., Syah, I. S. K., Megantara, S., & Chaerunisaa, A. Y. (2024). Nanotechnology-Enhanced Cosmetic Application of Kojic Acid Dipalmitate, a Kojic Acid Derivate with Improved Properties. Cosmetics, 11(1). https://doi.org/10.3390/cosmetics11010021

Boo, Y. C. (2019). Human Skin Lightening Efficacy of Resveratrol and Its Analogs: From in Vitro Studies to Cosmetic Applications. Antioxidants, 8(9). https://doi.org/10.3390/antiox8090332

Bothare, V. (2024). Skin Lightening Products Market Size, Share & Trends Analysis Report By Product (Creams, Cleanser, Mask, Others), By Nature (Synthetic, Natural, Organic) and By Region(North America, Europe, APAC, Middle East and Africa, LATAM) Forecasts, 2022-2030.

Burnett, C. L., Bergfeld, W. F., Belsito, D. V., Hill, R. A., Klaassen, C. D., Liebler, D. C., Marks, J. G., Shank, R. C., Slaga, T. J., Snyder, P. W., & Andersen, F. A. (2010). Final report of the safety assessment of kojic acid as used in cosmetics. International Journal of Toxicology, 29(6). https://doi.org/10.1177/1091581810385956

Castilla-Miguel, L., & Aramendia-Muneta, M. E. (2023). Digital Marketing Tools and Market Trends in the Skincare Industry: Consumer Behavior and Sales Growth Insights (pp. 235–268). https://doi.org/10.4018/979-8-3693-0551-5.ch011

Chen, Y.-M., Chen, L., Wen-Jing, Z., Yan, S., Zi-Jie, W., Qing-Xi, C., & and Wang, Q. (2019). Kinetic and computational molecular docking simulation study of novel kojic acid derivatives as anti-tyrosinase and antioxidant agents. Journal of Enzyme Inhibition and Medicinal Chemistry, 34(1), 990–998.

https://doi.org/10.1080/14756366.2019.1609467

Davis, E. C., & Callender, V. D. (2010). Postinflammatory Hyperpigmentation A Review of the Epidemiology, Clinical Features, and Treatment Options in Skin of Color. In J Clin Aesthetic Dermatol (Vol. 3, Issue 7).

Desai, S. (2014). Hyperpigmentation therapy: a review. Journal of Clinical Aesthetic Dermatology, 7(8), 13–17.

Gautam, M. (2023). Management of epidermal hyperpigmentation with a novel depigmenting formulation: a research survey. International Journal of Research in Medical Sciences, 11(9), 3365–3372. https://doi.org/10.18203/2320-6012.ijrms20232794

Ghasemiyeh, P., Fazlinejad, R., Kiafar, M. R., Rasekh, S., Mokhtarzadegan, M., & Mohammadi-Samani, S. (2024). Different therapeutic approaches in melasma: advances and limitations. In Frontiers in Pharmacology (Vol. 15). Frontiers Media SA. https://doi.org/10.3389/fphar.2024.1337282

Gillbro, J. M., & Olsson, M. J. (2011a). The melanogenesis and mechanisms of skin-lightening agents – existing and new approaches. International Journal of Cosmetic Science, 33(3), 210–221. https://doi.org/https://doi.org/10.1111/j.1468-2494.2010.00616.x

Gillbro, J. M., & Olsson, M. J. (2011b). The melanogenesis and mechanisms of skin-lightening agents – existing and new approaches. International Journal of Cosmetic Science, 33(3), 210–221. https://doi.org/https://doi.org/10.1111/j.1468-2494.2010.00616.x

Gonçalez, M. L., Marcussi, D. G., Calixto, G. M. F., Corrêa, M. A., & Chorilli, M. (2015). Structural characterization and in vitro antioxidant activity of kojic dipalmitate loaded W/O/W multiple emulsions intended for skin disorders. BioMed Research International, 2015. https://doi.org/10.1155/2015/304591

Kim, H. J., Kazi, J. U., Lee, Y. R., Nguyen, D. H., Lee, H. B., Shin, J. H., Soh, J. W., & Kim, E. K. (2010). Visualization of the melanosome transfer-inhibition in a mouse epidermal cell co-culture model. International Journal of Molecular Medicine, 25(2), 249–253. https://doi.org/10.3892/ijmm_00000337

Lajis, A. F. B., Hamid, M., & Ariff, A. B. (2012). Depigmenting effect of kojic acid esters in hyperpigmented B16F1 melanoma cells. Journal of Biomedicine and Biotechnology, 2012. https://doi.org/10.1155/2012/952452

Lee, M., Park, H. Y., Jung, K. H., Kim, D. H., Rho, H. S., & Choi, K. (2020). Anti-melanogenic Effects of Kojic Acid and Hydroxycinnamic Acid Derivatives. Biotechnology and Bioprocess Engineering, 25(2), 190–196. https://doi.org/10.1007/s12257-019-0421-y

Lee, Y. S., Park, J. H., Kim, M. H., Seo, S. H., & Kim, H. J. (2006). Synthesis of Tyrosinase Inhibitory Kojic Acid Derivative. Archiv Der Pharmazie, 339(3), 111–114. https://doi.org/https://doi.org/10.1002/ardp.200500213

Mohammadi, F., Giti, R., Meibodi, M. N., Ranjbar, A. M., Bazooband, A. R., & Ramezani, V. (2021). Preparation and evaluation of kojic acid dipalmitate solid lipid nanoparticles. Journal of Drug Delivery Science and Technology, 61, 102183. https://doi.org/https://doi.org/10.1016/j.jddst.2020.102183

Moharir, S., Khobragade, P., Rane, R., Suryawanshi, M., Pal, K., Gawade, B., Kumar, D., & Satpute, B. (2024). Discovery of Novel Diesters Incorporating Kojic Acid With NSAIDs and Palmitic Acid as Dual Inhibitor of Melanogenesis and Inflammation. Journal of Pharmaceutical Sciences, 113(7), 1769–1778. https://doi.org/https://doi.org/10.1016/j.xphs.2024.04.019

Nahhas, A. F., Abdel-Malek, Z. A., Kohli, I., Braunberger, T. L., Lim, H. W., & Hamzavi, I. H. (2019). The potential role of antioxidants in mitigating skin hyperpigmentation resulting from ultraviolet and visible light-induced oxidative stress. Photodermatology, Photoimmunology & Photomedicine, 35(6), 420–428. https://doi.org/https://doi.org/10.1111/phpp.12423

Pillaiyar, T., Manoj, M., & and Jung, S.-H. (2015). Inhibitors of melanogenesis: a patent review (2009 – 2014). Expert Opinion on Therapeutic Patents, 25(7), 775–788. https://doi.org/10.1517/13543776.2015.1039985

Qun, C., & Jing, W. (2008). Preparation method of novel whitening additive, i.e. kojic acid dipalmitate.

Saeedi, M., Eslamifar, M., & Khezri, K. (2019). Kojic acid applications in cosmetic and pharmaceutical preparations. Biomedicine & Pharmacotherapy, 110, 582–593. https://doi.org/https://doi.org/10.1016/j.biopha.2018.12.006

Sainakham, M., Promma, B., Ngernthong, A., Kiattisin, K., Boonpisuttinant, K., Wuttikul, K., Jantrawut, P., & Ruksiriwanich, W. (2024). Preparation and stability investigation of ultrasound-assisted W/O/W multiple nanoemulsions co-loaded with hydrophobic curcumin and hydrophilic arbutin for tyrosinase inhibition. Heliyon, 10(14). https://doi.org/10.1016/j.heliyon.2024.e34665

Sarkar, R., Arora, P., & Garg, Kv. (2013). Cosmeceuticals for hyperpigmentation: What is available? Journal of Cutaneous and Aesthetic Surgery, 6(1), 4. https://doi.org/10.4103/0974-2077.110089

Silpa-archa, N., Kohli, I., Chaowattanapanit, S., Lim, H. W., & Hamzavi, I. (2017). Postinflammatory hyperpigmentation: A comprehensive overview: Epidemiology, pathogenesis, clinical presentation, and noninvasive assessment technique. Journal of the American Academy of Dermatology, 77(4), 591–605. https://doi.org/10.1016/j.jaad.2017.01.035

Syed Azhar, S. N. A., Ashari, S. E., Ahmad, S., & Salim, N. (2020). In vitro kinetic release study, antimicrobial activity and in vivo toxicity profile of a kojic acid ester-based nanoemulsion for topical application. RSC Adv., 10(71), 43894–43903. https://doi.org/10.1039/D0RA04807K

Tanveer, N., Khan, H. M. S., & Akhtar, N. (2022). Whitening effect of kojic acid dipalmitate loaded nanosized ethosomal gel for the treatment of hyperpigmentation: In vitro and in vivo characterization. Journal of Cosmetic Dermatology, 21(12), 6850–6862. https://doi.org/https://doi.org/10.1111/jocd.15408

Tazesh, S., Tamizi, E., Shadbad, M. S., Mostaghimi, N., & Monajjemzadeh, F. (2022a). Comparative Stability of Two Anti-hyperpigmentation Agents: Kojic Acid as a Natural Metabolite and Its Di-Palmitate Ester, Under Oxidative Stress; Application to Pharmaceutical Formulation Design. Advanced Pharmaceutical Bulletin, 12(2), 329–335. https://doi.org/10.34172/apb.2022.031

Tazesh, S., Tamizi, E., Shadbad, M. S., Mostaghimi, N., & Monajjemzadeh, F. (2022b). Comparative Stability of Two Anti-hyperpigmentation Agents: Kojic Acid as a Natural Metabolite and Its Di-Palmitate Ester, Under Oxidative Stress; Application to Pharmaceutical Formulation Design. Advanced Pharmaceutical Bulletin, 12(2), 329–335. https://doi.org/10.34172/apb.2022.031

Zilles, J. C., Duarte, L. P., Ruaro, T. C., Zimmer, A. R., Kulkamp-Guerreiro, I. C., & Contri, R. V. (2023). Nanoemulsion Containing

Kojic Dipalmitate and Rosehip Oil: A Promising Formulation to Treat Melasma. Pharmaceutics, 15(2). https://doi.org/10.3390/pharmaceutics15020468

Zolghadri, S., Asieh, B., Mahmud Tareq, H. K., J., M.-M., F., G.-M., F., G.-C., & and Saboury, A. A. (2019). A comprehensive review on tyrosinase inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry, 34(1), 279–309. https://doi.org/10.1080/14756366.2018.1545767