Review

A Comprehensive Review of the Cosmetic Application of Kojic Acid Dipalmitate: Kojic Acid Derivative with Improved Properties

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A Comprehensive Review of the Cosmetic Application of Kojic Acid Dipalmitate: Kojic Acid Derivative with Improved Properties

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Abstract: Kojic acid (KA) has emerged as a prominent tyrosinase inhibitor with considerable potential in cosmetic applications; however, its susceptibility to instability during storage poses a challenge to its widespread use. This review explores the advancements in addressing this limitation through the development of various KA derivatives, focusing on the modification of the C-7 hydroxyl group. Strategies such as esterification, hydroxy-phenyl ether formation, glycosylation, and incorporation into amino acid or tripeptide derivatives have been employed to enhance stability and efficacy. Among these derivatives, Kojic Acid Dipalmitate (KDP), a palmitic ester derivative of KA, stands out for its notable improvements in stability, permeability, and low toxicity. Recent developments indicate a growing utilization of KDP in cosmetic formulations, with over 132 available products on the market, encompassing various formulations. Additionally, three patents and seven advanced system deliveries of KDP further underscore its significance. Despite its increasing prevalence, the literature on KDP remains limited. This comprehensive review aims to bridge this gap by providing insights into the synthesis process, physicochemical properties, pharmaceutical preparation, diverse applications of KDP in cosmetic products, and recent nanotechnology formulations of KDP. This review paper seeks to explore the recent developments in the use of KDP in cosmetics. The goal is to enhance stability, permeability, and reduce the toxicity of KA, with the intention of promoting future research in this promising sector.

Keywords: kojic acid dipalmitate; cosmeceuticals; cosmeceuticals

1. Introduction

Tyrosinase (monophenol, L-dopa: oxygen oxidoreductase, EC 1.14.18.1) known as the starting point for the formation of mammalian skin color [1]. It is an enzyme that catalyzes several steps in the production of the pigment melanin in living cells, including bacteria, fungi, plants, animals, and humans [1,2]. It is located in melanocytes in the epidermis, especially in the viable epidermis [3,4]. Tyrosinase is the enzyme that controls the pace of melanin synthesis [6], which is the process responsible for producing the pigment that determines skin color [7].

Melanin synthesis, or melanogenesis, is a complex process that involves various protein groups, including tyrosinase, tyrosinase-related protein 1 (Tyrp1 or TRP1), and tyrosinase-related protein 2 (Tyrp2, DCT, or TRP2) [6–8]. Melanogenesis occurs in an auto-regulated manner. The activity of tyrosinase begins with the presence of the substrate tyrosine and the enzyme co-factor, dihydroxyphenylalanine (DOPA).

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Tyrosinase uses its binuclear copper center to hydroxylate tyrosine into 3,4-dihydroxyphenylalanine (DOPA) [9,10]. Then, tyrosinase catalyzes the oxidation of DOPA to DOPAquinone [13]. This reaction proceeds with multi-polymerization to form pigments that are blackish-gray in color, namely eumelanin, and red-yellowish in color, namely pheomelanin, with the influence of the conjugation reaction [14].

This melanogenesis process occurs in the melanosome [15], where the size, density, and shape of the melanosome among populations have the same characteristics [11,16]. The determinant of skin color for a population is the total amount, ratio, and distribution of eumelanin and pheomelanin, which differ among populations around the world, such as Europe, Africa, and Asia [17]. In some countries, particularly in Southeast Asia, a high amount of eumelanin is undesirable because fair and clean skin has become the standard of beauty for women in these countries [11,12]. This is evident from a study by Peltzer (2016) of 19,624 students from 26 low-, middle-, and developing-income countries, showing that Southeast Asia has a higher percentage of skin-lightening product users than Africa, at 36.0% [18]. Indonesia, with a majority of Fitzpatrick skin phototypes IV and V, which tend to be dark or brown [18], has a skin-lightening product usage rate of up to 36% [19]. Abnormal skin pigmentation in the form of hypo- or hyperpigmentation can cause significant anxiety and decrease self-esteem in affected individuals [18,19]. Various methods are employed to regulate pigmentation in the fields of dermatology and cosmetics. One of these methods involves the utilization of synthetic compounds, such as hydroquinone and kojic acid (KA) [22]–[24].

Hydroquinone is a gold standard compound for treating hyperpigmentation [20–22]. However, its use in cosmetic formulations is prohibited due to the side effects such as irritation, allergic reactions, post-inflammatory hyperpigmentation, and temporary hypopigmentation that it can cause [14–18]. Hydroquinone ($C_6H_6O_2$) reduces the level of pigmentation by non-selectively degrading epidermal melanocytes and keratinocytes, making it cytotoxic to cells [28,29]. Therefore, the use of skin-lightening agents in cosmetic formulations has shifted towards more effective alternative compounds with low toxic and irritation effects, such as kojic acid [20,30].

Kojic acid is one of several tyrosinase inhibitors that have been extensively studied for this purpose [24–27]. It is a natural compound with both skin-lightening and antibacterial properties and is widely used for cosmetic purposes and as a food additive to prevent browning caused by enzymes [20–22]. While KA has a competitive inhibitory effect on the monophenolase activity and a mixed inhibitory effect on the diphenolase activity of mushroom tyrosinase, its use in cosmetics is limited by its instability during storage due to its labile oxidative properties, which can be accelerated by light and heat [34]. To address these limitations, various KA derivatives have been developed by modifying the C-7 hydroxyl group, such as through esterification [42], hydroxyphenyl ether formation [43], glycosylation [44], or incorporation into amino acid or tripeptide derivatives [45], with the aim of improving their stability and efficacy in cosmetic and cosmeceutical applications.

According to reports, kojic acid-tripeptide amide derivatives have shown superior storage stability in comparison to kojic acid [46]. Additionally, as stated in Rho et al. (2010) [47], kojyl thioether derivatives strongly inhibit tyrosinase activity. Moreover, Lee et al (2006) [44] report that kojic acid derivatives with two pyrone rings possess eight times higher tyrosinase inhibitory potency than kojic acid itself. Maltol (3-hydroxy-4H-pyran-4-one) and its derivatives share a similar scaffold with kojic acid and have similar biological effects. Ester derivatives of allomaltol (5-hydroxy-2-methyl-4H-pyran-4-one) have been described to have inhibitory to tyrosinase and antioxidant effects by Wempe et al. in Michael (2012) [48]. Kojic acid has also been reported to exhibit antioxidant activity [49]. According to Ahn el al. (2011), a kojic acid derivative containing a trolox moiety exhibits potent tyrosinase inhibitory and radical scavenging activity [50]. Lajis et al., 2012 suggest that KA esters derived from the esterification of kojic acid and palm oil-based fatty acids, namely kojic acid monooleate, kojic acid monolaurate, and kojic acid monopalmitate, was exhibit similar inhibitory effects to kojic acid; however, kojic acid monopalmitate gave slightly stronger inhibition to melanin formation compared to other inhibitors [40]. Moreover, Balaguer et al. (2008) reported that kojic acid dipalmitate (KDP) poses superior stability, oil solubility, and skin absorption compared to kojic acid, attributed to its resistance to changes in pH, heat, and light compared to kojic acid [34].

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Kojic Acid Dipalmitate (KDP), a palmitic ester derivative of KA, has gained widespread usage in cosmetic formulations in recent times due to its improvement in stability and permeability, as well as its low toxicity [19,21,31]. It is synthesized in skin cells through an *in-situ* esterification process, which results in the release of kojic acid [52]. This unique characteristic sets it apart from other derivatives of kojic acid [53]. The aforementioned condition has resulted in the widespread usage of KDP, which is a commonly utilized component in numerous skincare items, including creams and serums, by well-known cosmetic brands. These products usually contain concentrations of up to 3% KDP and are marketed as skin-whitening and lightening agents [54]. Despite its widespread use, the available literature on KDP remains limited. This review aims to discuss various aspects of KDP, including its synthesis process, physicochemical properties, pharmaceutical preparation, and application in cosmetic products. Although KDP is becoming more common, there is still a scarcity of literature on the subject. This thorough review seeks to fill this need by offering insights into the synthesis process, physicochemical features, pharmaceutical preparation, and many uses of KDP in cosmetic goods. This review study aims to examine the latest advancements in the use of KDP in the field of cosmetics. The objective is to improve the stability, permeability, and toxicity of KA in order to facilitate further investigation in this promising field.

2. Sythesis of Kojic Acid Dipalmitate

The hydrophilicity of KA has limited its use in cosmetics, oily foods, and pharmaceutical products. Furthermore, concerns exist regarding its potential toxicity [54] and irritancy [50–52]. To enhance the chemical and biological attributes of KA, researchers have developed derivatives with improved properties. Several efforts, including the enzymatic esterification of KA and fatty acids to form KA esters, have been undertaken [57] to increase their hydrophobicity and expand their potential uses, such as in the cosmetic industry. Some KA esters, like KA dipalmitate, have been brought to market for cosmetic and skin health applications [58].

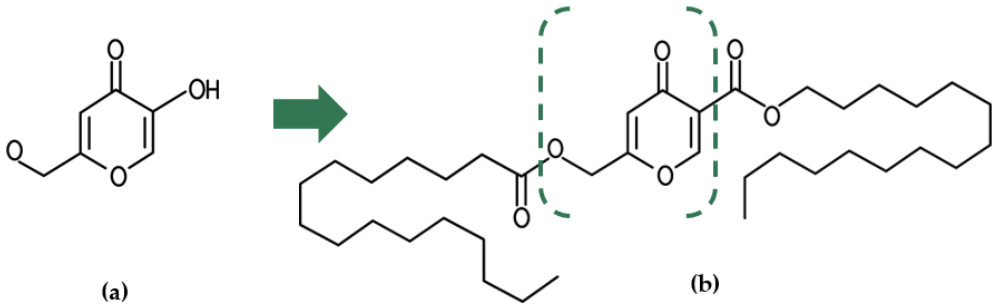

Figure 1. The basic molecular structure of (a) kojic acid and (b) kojic acid dipalmitate.

Kojic acid dipalmitate can be synthesized by esterifying kojic acid with palmitic acid. Figure 1 depicts the basic molecular structure of KA and KDP. Kojic acid possesses two functional groups: a hydroxyl group (OH) at C-5 and a carboxylic group (COOH) at C-7 [59]. The esterification process involves removing the OH group and attaching the fatty acid (R) to create KA monoesters like 5-O-KA monoesters and 7-O-KA monoesters. Fatty acids have been synthesized chemically and enzymatically to link with KA at positions C-5 and C-7 [60]. Chemical esterification of KA oleate was facilitated by N,N′-dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP) in dichloromethane, resulting in yields of up to 80% within 24 to 48 hours. However, this method necessitates the use of environmentally harmful and dangerous chemicals, requiring additional safety precautions. Other chemical esterification procedures involve numerous steps and chemicals, leading to a higher production cost for KDP [40].

Enzymatic processes for esterification of KA involve the preparation and catalysis of lipases and proteases in organic or solvent-free systems, resulting in the utilization of fewer chemicals and being more cost-effective and environmentally friendly. When used in their immobilized form, most of the enzymes can be repeatedly reused, resulting in consistent specific enzyme activity and yield during the synthesis

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of KA esters. The yield of enzymatically synthesized KA esters is influenced by several factors, including the type of catalytic enzyme, reaction temperature, organic solvents, KA to fatty acid ratio, metal ions, water content, and pH [40,61,62].

Various enzymes have been screened for enzymatic synthesis of KA esters, and most of them were derived from fungi and bacteria. However, the highest yields were obtained when lipase enzymes from *Candida antarctica, Pseudomonas cepacia,* and *Rhizomucor miehei* were utilized. Based on research conducted by Liu and Shaw (1998) [61], Kobayashi et al. (2001) [63], Khamaruddin et al. (2008) [64], and Ashari et al. (2009) [57], the synthesis of C-5-KA monoester using these enzymes resulted in a yield of 40-60%. The optimal temperature for KA ester synthesis is closely linked to the optimum temperature of the immobilized enzyme employed in the esterification process. For instance, lipase from Pseudomonas cepacia exhibits its optimal activity at a temperature of 50°C [61,62]. In this context, immobilized enzymes are utilized due to their thermostability and higher catalytic activity when compared to free enzymes [65]. Furthermore, the choice of an organic solvent played a significant role in influencing the esterification process. A high ratio of KA to fatty acids esterification resulting in KA esters was attained by using specific solvents, namely acetonitrile, acetone, and chloroform, which possessed logP values of -0.33, -0.21, and 2.00, respectively [66]. To enhance the hydrophobic nature of the reaction mixture and thereby improve the efficiency of the esterification process, a co-solvent mixture was also employed [66]. Moreover, KA to fatty acid ratio, metal ions, water content, and pH also influence the esterification process. Lajis et al. (2013) [62] have extensively discussed the influence of these parameters on esterification. Readers are encouraged to refer directly to the literature for more details.

3. Physical and Chemical Propreties of Kojic Acid Dipalmitate

The molecular formula of kojic acid dipalmitate (2-Palmitoyloxymethyl-5-palmitoyloxy-pyrone) is $C_{38}H_{66}O_6$ with a molecular weight of 618.9 g/mol [67]. Kojic dipalmitic acid exhibits characteristics of a white powder [52], a melting point of 94°C, and solubility in oil, alcohol, mineral oil, and esters. Unlike kojic acid, kojic acid dipalmitate is more stable to light, heat [68], and oxidation and does not chelate metal ions [69]. This makes it more color-stable with a reduced likelihood of turning yellow or brown, which makes it a more popular choice for manufacturers of skin-lightening whitening creams [69]. Kojic acid dipalmitate is also considered stable over a wide range of pHs [70].

The chemical structure of kojic acid dipalmitate consists of two molecules of palmitic acid, which are saturated fatty acid, attached to the two hydroxyl groups of kojic acid. This structure gives kojic acid dipalmitate its lipophilic (fat-loving) properties, making it more soluble in oils and fats than kojic acid itself [52,71]. These derivatives have been found to improve both the stability and solubility of kojic acid in oily cosmetic products [72].

Based on acomparative stability study conducted by Tazesh et al. (2019) between KA and KDP under oxidative stress, it was observed that KDP underwent more rapid degradation in similar liquid oxidative stress conditions compared to KA [52]. This degradation could possibly be linked to the opening of the pyrone ring, followed by subsequent decomposition into smaller aliphatic chains. Based on the study, it was concluded that the notion of enhancing the stability of KA by obstructing its hydroxyl groups through the attachment of two palmitic acid molecules was a misconception, as the hydroxyl groups are not the reactive moiety of the molecule. However, Tazesh et al. (2019) still recommend choosing KDP over KA in cosmetic formulations. Yet, to prevent oxidation, formulators can include antioxidants to achieve improved stability results [52].

4. Mechanism of Action of Kojic Acid Dipalmitate

Kojic Acid Dipalmitate (KDP) demonstrates greater effectiveness compared to KA [35]. Esterases within skin cells hydrolyze KDP, leading to the *in-situ* release of kojic acid, as illustrated in Figure 2 [34]. Consequently, the mechanism of action for KDP is akin to that of KA. The depigmentation properties of kojic acid, elucidated from cellular to molecular levels, have been extensively explored by Saeedi et al. (2019) [35].

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Kojic acid, extensively studied as an inhibitor of tyrosinase, is recognized for its competitive inhibition of monophenolase activity and its mixed inhibitory effect on the diphenolase activity of mushroom tyrosinase [73]. Due to the action mechanism described, kojic acid is categorized as a "true inhibitor," wherein it can bind to the enzyme and inhibit tyrosinase activity. Tyrosinase is a copper-containing monooxygenase enzyme that catalyzes two reactions: o-hydroxylation of monophenols to catechols, also known as monophenolase or cresolase activity, and oxidation of catechols by O_2 to o-quinones, known as diphenolase or catecholase activity. Typically, true inhibitors are classified into four types: competitive inhibitors, uncompetitive inhibitors, mixed-type (competitive/uncompetitive) inhibitors, and non-competitive inhibitors (Figure 3). Competitive inhibitors are compounds that can bind to free enzymes, thereby preventing substrates from binding to the enzyme. The observed competitive inhibitory effect of kojic acid is attributed to its ability to chelate copper at the enzyme's active site. In contrast to competitive inhibitors, uncompetitive inhibitors can bind only to the enzyme-substrate complex. A mixed-type inhibitor, which is both competitive and uncompetitive, can bind to both the free enzyme and the enzyme-substrate complex. Most mixed-type inhibitors bind to a free enzyme and an enzyme-substrate complex with the same equilibrium constant. In addition to the inhibitory mechanism, the strength of inhibition is a primary criterion for an inhibitor [73].

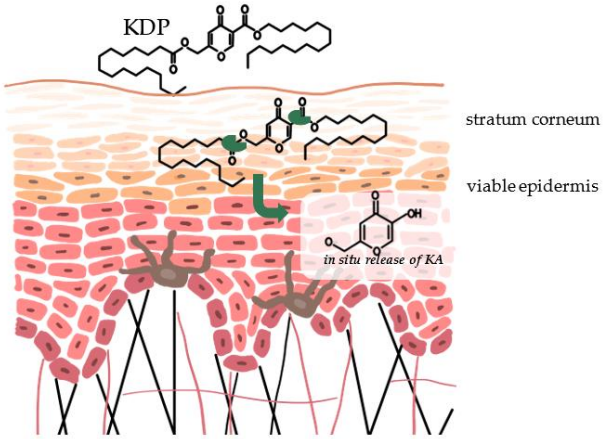

Figure 2. *In-situ* liberation of KA. The enzymatic activity of esterases in the skin leads to the *in-situ* liberation of kojic acid from KDP. This process takes place within the viable epidermis.

Casella et al. [74] studied how KA affects the oxidation of 3,5-dtbc (3,5-di-tert-butyl catechol) by dicopper model complexes. They suggested that KA acts as a connecting bridge between the metal centers in the dicopper(II) catalysts, indicating that KA may bind to the dicopper Ty center. This idea gained support from two other reports that characterized tetrachloro-o-catecholate-bridged dicopper(II) complexes [75]. Subsequent reports by Plenge et al. [76] and Ackermann et al. (2002) [77] put forward the concept of bridging and unsymmetric binding of catechol substrates in a Z2:Z1 fashion, with one of the two oxygen atoms participating in a weak interaction with either of the neighboring copper(II) ions. Studies involving electron spin echo envelope modulation (ESEEM) [78] and X-ray absorption spectroscopy (XAS) [79] of a met Ty-KA adduct from bacterial *Streptomyces antibioticus* Ty provided further support for this binding mechanism. However, when the X-ray structure of the adduct of KA with the met form of Bacillus megaterium Ty was examined, it revealed that the KA molecule was situated at a distance of 7 Å from the dicopper center. This finding contrasted with the conclusions of Bochot et al. (2013) [80], who reported that the distances between copper and oxygen atoms of KA varied around 2.15 Å for CuB···O2, 2.04 Å for CuA···O2, and 2.17 Å for CuA···O3 [80].

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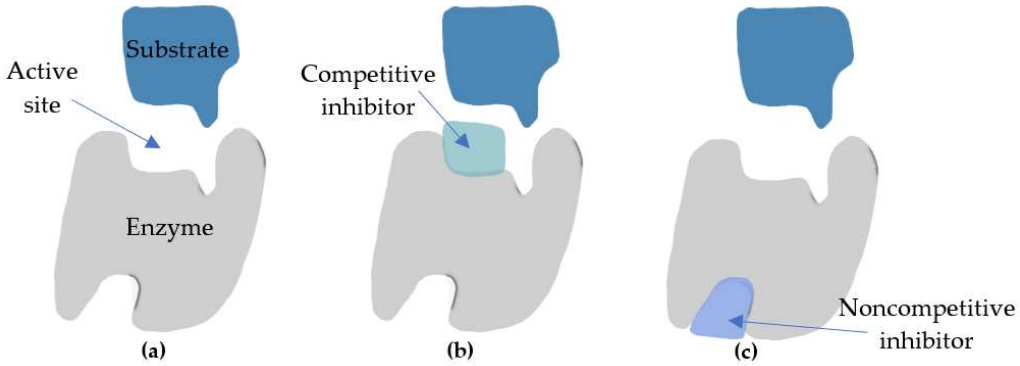

Figure 3. True inhibitors mechanisms of action: (a) normal binding; (b) competitive inhibition; (c) noncompetitive inhibition.

Moreover, kojic acid has been reported as a slow-binding inhibitor of tyrosinase's diphenolase activity. Other potent slow-binding inhibitors of tyrosinase include tropolone and the substrate analog L-mimosine. Interestingly, all these slow-binding inhibitors of tyrosinase share a common feature: they contain an α-hydroxyketone group. Kojic acid, tropolone, and L-mimosine are frequently used as positive controls in the literature to compare the inhibitory potency of newly discovered inhibitors [73].

5. Cosmetic Application of Kojic Acid Dipalmitate

5.1. Cosmetic Products Containing KDP

In skincare products, kojic acid dipalmitate was used at concentrations ranging from 0.01% to 25%. Typically, it was employed at concentrations between 0.2% and 8.0%, with the most frequent usage occurring at concentrations of 0.4% to 4.0% [81]. Kojic acid dipalmitate exhibited the ability to inhibit the activity of the tyrosinase enzyme, thereby decelerating melanin synthesis by impeding the conversion of DOPAchrome into DHICA [40].

A study conducted by Chandrashekar et al. in 2018 demonstrated that a 2% kojic acid dipalmitate formulation in a combination cream was effective and safe as a therapy for melasma. Kojic acid dipalmitate did not induce skin irritation and contributed to skin brightening, as evidenced by a reduction in hyperpigmentation observed in 51-57% of the subjects. Kojic acid at concentrations of 1-2% did not exhibit hepatocarcinogenic effects, was non-genotoxic, did not irritate the mucosal layer, and did not lead to sensitization [36,82].

As of the time when this literature review was conducted, it is known that there are over 132 cosmetics available on the market containing Kojic Acid Dipalmitate (KDP) in various formulations. This data was obtained from a list of products containing kojic acid dipalmitate accessed on the website [83]. These formulations include face or body creams, lotions, gels, face masks, serums, toners, eye-brightening products, lip products, face or body washes, and soap bars, as well as underarm creams designed to reduce pigmentation. All of these have been summarized in Figure 3.

The concentrations of KDP in these products typically range from 0.4% to 4.0%. KDP is most commonly formulated in creams designed for brightening both facial and body areas. In contrast, formulations containing KDP as face scrub and lip scrub are relatively rare. Additionally, KDP is incorporated into cosmetics intended for the whitening of the under-eye area and the lightening of the underarms. In addition to containing KDP, these whitening products may be provided as standalone treatments or in combination with other depigmenting agents such as arbutin, niacinamide, retinol, tranexamic acid (an antifibrinolytic agent widely favored in cosmetics for addressing melasma or hyperpigmentation), or in combination with exfoliant agents like glycolic acid and lactic acid. These products may also include antioxidants such as ascorbic acid and tocopherol acetate, as well as pine bark extracts [83].

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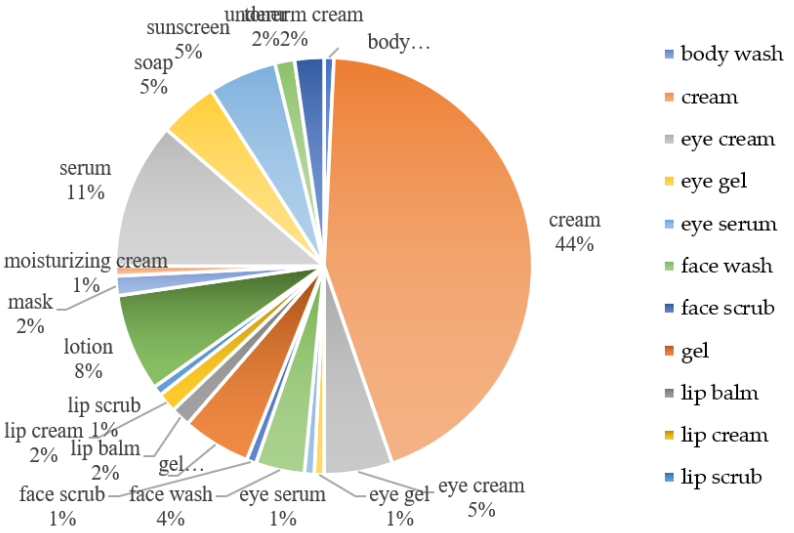

Figure 3. Cosmetics available in the market containing Kojic Acid Dipalmitate (KDP) in various formulations.

3.3. Patent Products of KDP

The patents related to kojic acid dipalmitate remain relatively limited. One such patent related to KDP is the US patent held by Whittemore et al. (1998), which claims a skin-whitening cosmetic composition containing kojic dipalmitate. The invention specifically pertains to an anhydrous skin-whitening cosmetic composition incorporating kojic dipalmitate [84].

The Shanghai Institute of Technology holds a patent for Solid Lipid Nanoparticles (SLN) containing kojic acid dipalmitate, valid until 2014. A disclosed innovation pertains to a nanometer-sized solid lipid carrier encapsulating kojic acid dipalmitate. This delivery system was designed to enhance the permeation of kojic acid dipalmitate into the skin, increase utilization efficiency, and improve the whitening effect components.

Table 1. Patents of kojic acid dipalmitate.

Pantent's holder	Field of Invention	Year	No. of patent	Refference
Jerry Whittemore Robert Neis	The present invention relates to a skin-whitening cosmetic compositions and in particular to such a composition that is anhydrous and incorporates kojic dipalmitate.	1998-2018	US5824327A	[84]
Shanghai Institute of Technology	A kind of nano-solid lipid carrier and preparation method of coated kojic acid acid dipalmitate	2014-2034	CN104116643A	[85]
Shanghai Jahwa United Co Ltd	The present invention relates to a kind of high-performance liquid chromatography (HPLC) analytical approach, be specifically related to method with the HPLC quantitatively analyzing kojic dipalmitate.	2002-2022	CN1188700C	[86]

Components of the formulation shown in the patent include kojic acid dipalmitate, phospholipid, solid lipid, liquid lipid, a solid emulsifying agent, a polyalcohol additive, and a preservative, with the remaining content being deionized water. The method for preparing the nanometer solid lipid carrier involves melting an oil phase and ingredients that dissolved in it at 75-95°C, heating a water phase containing deionized water and the polyalcohol additive, and combining the two phases. High-pressure homogenization is then performed, followed by stirring and cooling to produce the nanometer-sized solid lipid carrier [85].

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As for the patent regarding the analytical approach of Kojic Dipalmitate (KDP) using the High-Performance Liquid Chromatography (HPLC) method, it is held by Shanghai Jahwa United Co. Ltd. [86]. The three patented formulations and characterizations containing kojic acid dipalmitate are presented in Table 1.

6. Nanotechnology Formulations of Kojic Acid Dipalmitate

Nanotechnology refers to the manufacturing and use of materials at the nanoscale [87]–[89], where they exhibit distinct physicochemical characteristics compared to their larger particles [90]. These novel materials demonstrate an increased surface area as a result of certain internal rearrangements, leading to distinct interactions with biological systems [91]. The integration of nanotechnology into cosmetic formulations is regarded as the most current and developing technology currently accessible [88]. Cosmetic producers use nanoscale compounds to enhance UV protection [92]–[95], facilitate deeper skin penetration [96]–[100], prolong the effects [101,102], intensify color [103,104], improve finish quality [104], stability [101,105], and provide lower toxicity [98,106]. Kojic acid dipalmitate has been widely utilized in the cosmetics industry. It has been formulated using nanotechnology, primarily to enhance its physical and chemical properties.

Kojic acid dipalmitate incorporates two palmitate groups onto the hydroxyl group at C-7 [42], resulting in a molecular weight of KDP exceeding 500 Da, thereby impeding its permeability. As previously explained in the preceding section, the molecular weight of KDP is 618.9 g/mol [67]. According to the literature, a majority of chemical compounds with a molecular weight greater than 500 Da are unable to permeate the skin through passive diffusion processes [107]. To address this limitation, KDP has been formulated into various preparations such as nanosomes, nanocreams, multiple emulsions, liposomes, solid lipid nanoparticles (SLN), ethosomal suspensions, and nanoemulsions. These formulations aim to enhance skin permeability, stability, and reduce toxicity, thereby improving efficacy and conferring skin benefits. Figure 4 displays schematic representations of the architectures of KDP integrated into several types of nanomaterials.

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Table 2. Anhance cosmeceuticals formulation of KDP.

Published in	Preparation of KDP	The research objective	Diameter of particle/droplet	Zeta Potentials	Loading capacity	Results	Refference
2000	Nanosome	Development of KDP nanosome in mono-vesicle and increase stability	57-75,7 nm	-24mV	NA	Turbidity was very good transparency compared nanosome with liposome. It formed the monovesicle in the opposite direction to form the multi-lamelar vesicle of the liposome. The stability of nanosomes was very good for 6 months	[108]
2010	Nanocream	Increased release and permeability through skin *in vitro*	< 350 nm	NA	NA	nano-creams had shown to produce a higher drug release and permeability through Franz diffusion cells, although there was no significant variation than that in normal cream at P value < 0.05. Nano-creams penetrate faster and the cumulative amount of KDP is higher than in normal creams	[58]
2015	W/O/W Multiple Emulsions	Increase safety and activity of KDP *in vitro*	0,056µm-12.487µm	NA	N/A	Incorporation of KDP into MEs improved the safety and antioxidant activity of KDP *in vitro*	[71]
2020	Liposome	Increasing stability and loading capacity	80-100 nm; PDI ≤ 0.2	-0.5 to -0.6 mV	0.61% to 28.12 %	Ethosomal gel had a good stability at lower temperature (8, 25°C). KDP loading capacity increased from 0.61 to 28.12%	[109]
2020	Solid Lipid Nanoparticle (SLN)	Increase release profile and permeability through skin *ex vivo*	70 nm	NA	47%	The KDP loaded in the SLN presented a slower release profile of KDP in comparison with the formulations loaded with KDP. The KDP loaded into SLN had the highest concentration in the stratum corneum.	[53]
2022	Ethosomal suspension	Increases stability and skin benefits	148 nm	−23.4 mV	90.0008%	Ethosomal gel gave a significant decrease in skin melanin, erythema, and sebum levels while improving in skin hydration level and elasticity during non-invasive *in vivo* studies. The formulation had good stability at a lower temperature (8, 25°C).	[106]
2023	Nanoemulsion	Increase permeation, antioxidant and depigmentation efficiency, and lower cytotoxicity	< 130 nm	-10mV	> 95%	The nanoemulsion containing 1 mg/mL KDP exhibited antioxidant and depigmenting activities and allowed the active compound to reach the epidermis without permeating to deeper layers of the skin, showing potential for use in cosmetic formulations for melasma treatment. Such nanoemulsion was safe for fibroblast-like cells (3T3-L1) at concentrations up to 1%.	[110]

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6.1. Nanoemulsion

Zilles et al. (2023) are one of the researchers who have formulated the incorporation of KDP in nanoemulsions [110]. The study suggests that nanoemulsions serve as effective carriers, enhancing both the stability [111] and activity [58] of KDP on the skin. Beyond their carrier capabilities, nanoemulsions are recognized as a preferable option for drug delivery systems related to skin permeation. This preference arises from their diminished particle sizes and lipophilic characteristics [112], resulting in an increased affinity with the stratum corneum. Consequently, this facilitates deeper penetration and permeation of active substances into the skin, leading to heightened efficacy [113]. Additionally, nanoemulsions possess lipophilic cores, making them excellent carriers for hydrophobic actives in aqueous media [113].

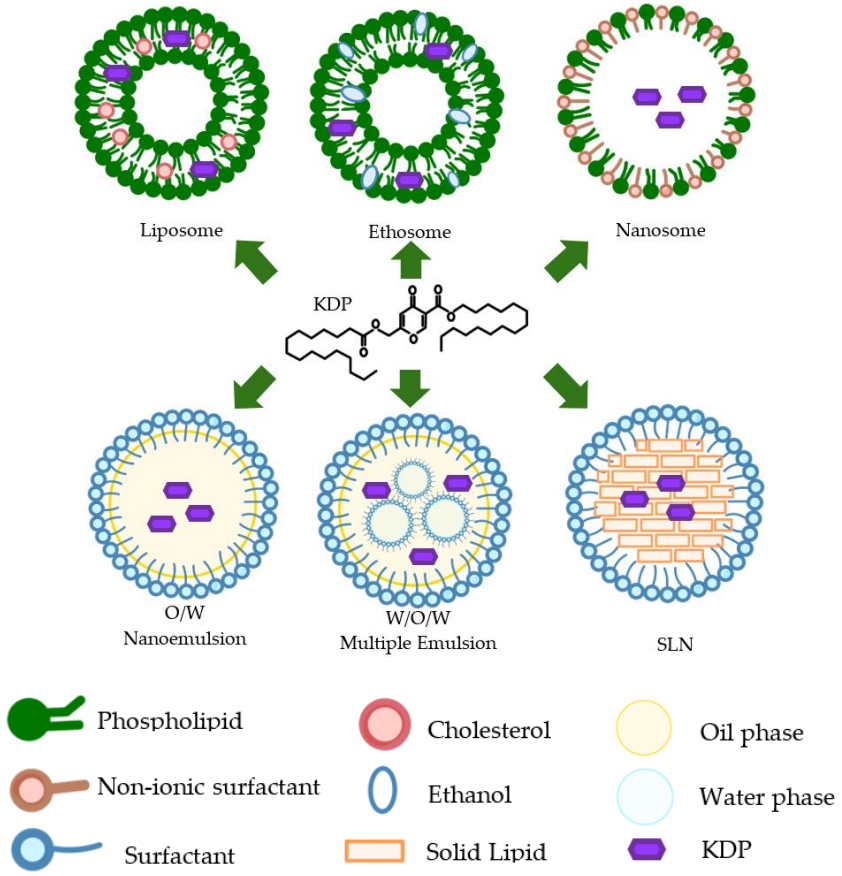

Figure 4. Schematic illustration of several configurations in which KDP nanomaterials were formulated.

6.2. Nanocream

Kojic acid dipalmitate (KDP) was also formulated in nanocream [111]. Nanocream is aformulation of nanoemulsion in the form of semisolid cream [114,115]. Nano-emulsions are composed of an isotropically clear dispersion of two liquids that are immiscible with each other with droplet size varied between 100 and 200 nm [116,117], in another literature, 600 nm [114]. These liquids include a disperse phase consisting of oils and a continuous phase consisting of water. The presence of dispersed phase droplets that are smaller than 200 nanometers results in the nanoemulsion exhibiting a clear and transparent appearance [118]. The stability of this dispersion is maintained by an interfacial film of surfactant molecules, which possess stable thermodynamic properties [107,119].

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Al-Edresi and Baie (2009) conducted a study aimed at formulating a nanoemulsion in cream form containing Kojic Acid Dipalmitate (KDP) as a whitening active ingredient and evaluating its stability [111]. The primary components of the nano-cream formulation included Emulium Kappa® (EK), which consists of candelilla/jojoba/rice bran polyglyceryl-3-esters, glyceryl stearate, stearoyl alcohol, and sodium stearoyl lactylate, serving as the emulsifier. Propylene glycol was used as a cosurfactant in a 9:1 ratio. The oil Phase comprised virgin coconut oil (VCO) and squalene oil, maintaining a consistent surfactant-to-oil ratio of 1.4:1.2. The formulation of the nanoemulsion was successfully achieved using the Emulsion Inversion Point method.

To mitigate Ostwald ripening, the main instability mechanism of emulsion systems [112], insoluble oil (squalene)-was added to the system. The Ostwald ripening rate decreased significantly from 14.94 to 0.97 nm/day as the squalene concentration increased from 2 to 20%, representing a nearly 15-fold reduction in growth rate. This finding aligns with the study done by Cruz-Barrios (2014), which demonstrates that the inclusion of squalene in the formula mitigates the impact of ripening [120]. The zeta potential of the formulation indicated an increase in charge from −65.1 to −101.8 mV with the rising squalene ratio. This led to enhanced repulsion forces between the droplets, contributing to the improved stability of the nanoemulsion [121]. The negative droplet charge resulted from the adsorption of hydroxyl ions on the non-polar VCO droplet through hydrogen bonding [122]. The primary droplet diameter, ranging from 171.3 to 240.2 nm, remained unaffected by the squalene ratio. It is important to note that while this research focused on enhancing the stability of the nanocream in terms of the zeta potential of the system, it did not assess the permeation of active ingredients into the skin [111]. In the subsequent development, Kojic acid dipalmitate (KDP) was further developed into an encapsulated form using phospholipids, namely liposomes [109].

6.3. Liposome

Al-Edresi et al. (2020) conducted a study to enhance the loading capacity of kojic acid dipalmitate (KDP) into liposomes using the active loading method [109]. In this research, KDP was formulated in liposomes as encapsulating agents to overcome obstacles to cellular uptake [123]–[125] and target specific sites *in vivo* [126,127] thereby improving the delivery efficacy of compounds. Liposomal formulations were also proposed as a means of enhancing the therapeutic efficacy of poorly bioavailable drugs [128,129].

Initially, liposomes were prepared using the thin lipid film hydration method without active ingredients. To actively load KDP into the liposomes, a KDP solution was mixed with liposome suspension in a shaking water bath at 60 ºC [130]. As the temperature of the liposomes increased to the phase transition temperature, holes opened in the lipid bilayer, allowing KDP to permeate from the intraliposomal to the interliposomal medium due to concentration gradients. This gradient served as a driving force for the permeation of KDP, leading to an equilibration of concentration on both sides of the liposome bilayer [131]. Active loading resulted in significantly higher loading capacity (%LC) compared to passive loading of KDP [126,131]. The concentration gradient technique forced KDP to be incorporated into the core of the liposomes, achieving an LC% of 28.12% [109].

Passive loading of KDP into liposomes, on the other hand, depended mainly on hydrophobic interaction and association with the 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) bilayer structure as a phospholipid [131]. Liposomes were able to incorporate KDP, but in low percentages for passive loading methods, with a loading capacity of 0.61%, as the lipid bilayer constituted only small fractions of the liposomes.

Using the active loading method not only resulted in an increase in the amount of KDP incorporated into the liposomes but also maintained stable liposomes with particle sizes in the range of 80-100 nm, PDI ≤ 0.2, and zeta potential of -0.5 to -0.6 mV [109]. No significant changes in particle size over time were observed, indicating stable liposomes. However, it's important to note that this study did not conduct penetration testing into the skin or evaluate the content of formulations during storage stability testing.

6.4. Solid Lipid Nanoparticles

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Solid lipid nanoparticles (SLNs), formerly referred to as lipospheres, are a kind of pharmaceutical nanocarrier that show potential for controlled drug delivery [132,133]. SLNs are generally composed of biodegradable and safe lipidic components [134]. SLNs possess the notable ability to transport a wide range of therapeutic substances, such as tiny medication molecules, big biomacromolecules (such as polysaccharides), genetic material (such as DNA or siRNA), and vaccination antigens [135]. Small drug molecules have the ability to load both hydrophilic and lipophilic medicines, including KDP.

Kojic Acid Dipalmitate (KDP) have been formulated in SLN by Mohammadi et al., (2020) [53]. SLN-loaded KDP formulation consisted of melted GMS 100 mg and KDP 10 mg in 2% PVA ( ) using evaporated solvent ethanol/aceton 2.5:1.5, all of which had a KDP entrapment efficiency of about 47%, meaning the KDP concentration in the formulation was 10 mg/25 ml (0,04%) and being loaded in the SLN of about 47% of 0.04% (0.02% KDP in SLN). SLN-loaded KDP was successfully formulated with the mean size of 70±5 nm. In this formulation, stability test results are not explained, so conclusions about the stability of the formula cannot be drawn. However, *in vitro* drug release and *ex vivo* permeation of Kojic Acid Dipalmitate (KDP) from Solid Lipid Nanoparticle (SLN)-based preparations were clearly described in the research paper.

The release profile of KDP from SLN preparations follows a first-order kinetic model. In comparison to KDP powder and KDP cream, formulations loaded with KDP in SLN, hydrogel, SLN-based cream, and SLN-based hydrogel exhibit a slower release rate. Among these, the KDP hydrogel demonstrates the slowest release profile, followed by the SLN-based hydrogel of KDP. These findings suggest that the lipophilic nature of KDP, the occlusive effect of the cream, the matrix structure of SLN, and the hydrogen bonds facilitated by polyvinyl alcohol (PVA) play crucial roles in determining the release rate of KDP and its diffusion into the receiving phase [53].

One of the factors accelerating the release rate from KDP powder and KDP cream is the lipophilic nature of KDP, which enable penetration into the skin through both intracellular and paracellular pathways. The second factor is the entrapment efficiency of KDP in the SLNs (47%). In contrast, KDP powder, KDP cream, and KDP hydrogel have higher concentrations, leading to a greater diffusion rate through the skin based on Fick's second law. The lipid matrix structure of SLNs retains lipophilic drugs for an extended period, allowing a slower release. The hydrogen bonds formed through the interaction of the hydrophilic structure of hydrogels, PVA in the SLNs, and even KDP itself contribute to a slower release rate from hydrogel formulations [53].

6.5. Ethosome

Kojic Dipalmitate (KDP) can also be formulated in nanosized ethosome gel. Various ethosomal suspensions loaded with KDP were prepared using soy phosphatidylcholine, ethanol, propylene glycol, and water through a cold method. These formulations underwent assessment for size, zeta potential, polydispersity index, entrapment efficiency, FTIR spectroscopy, and scanning electron microscopy (SEM). Subsequently, the stability of the optimized gel was examined, and in vivo studies were conducted to evaluate the skin benefits.

The optimized formulation has zeta potential, size, and entrapment efficiency of −23.4 mV, 148 nm, and 90.0008%, respectively. SEM results showed the vesicles were spherical in shape. Ethosomal gel had good stability at lower temperatures (8, 25°C). In addition, ethosomal gel causes a significant decrease in skin melanin, erythema, and sebum levels while it causes improvement in skin hydration level and elasticity during non-invasive in vivo studies [106].

The overall findings indicated that the prepared KDP-loaded ethosomal formulation was stable and provided deep penetration of KDP into the skin. It offers a promising therapeutic approach for use in skin hyperpigmentation as it has skin-whitening and moisturizing effects [106].

6.6. Nanosome

In the year 2000, In-young et al. introduced a novel encapsulation vesicle system that combines elements of both niosomes and liposomes, termed as nanosomes. Generally, when a surfactant is dissolved in water, it tends to form micelles [88,136]. A liposome is a molecule with two lipophilic

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parts attached, such as a phospholipid [137]. Furthermore, when phospholipids and surfactants are mixed and dispersed in water, a monolayer is formed in a lamellar structure, as opposed to micelles. These monolayer vesicles are denoted as nanosomes. In comparison to liposomes, these vesicles exhibit a much finer size, contributing to enhanced stability of the active ingredient [108].

In this study kojic acid dipalmitate was encapsulated inside the mono-layer vesicle and consisted of phospholipids and surfactants. The phospholipid used was hydrogenated liposomes (HL), and surfactants included in the formula were diethanolamine cetylphosphate (DEA-CP) and diglyceryl diodeate (DGDO). Kojic acid dipalmitate encapsulated in the vesicle could be up to 1% located in the core of the vesicles. With the application of the microfluidization (MF) method, the nanosomes was successfully developed until a nanosized suspension of the monovesicles system was obtained. It was confirmed through SEM that the particle size of the nanosomes was 57-75.7 nm, and the average particle size was 66nm, indicating very fine particle size was formed. The stability of nanosomes developed in this research was also good, because of they passed through MF three times as confirmed by the zeta potential value at 23.8 mV [108].

6.7. Multiple Emulsion

Kojic Dipalmitate (KDP) has also been formulated into multiple emulsions (MEs) with the aim of increasing their bioavailability and protecting the drugs against biological degradation and oxidation processes [72]. This formulation can extend the drug release, potentially reducing the required dosages and application time. The ME system formulated was in the form of a water-in-oil (W/O/W) system, developed through a two-step process. The initial W/O emulsion was first created using 20% span 80 as a surfactant, 45% liquid petrolatum, and 35% water. The primary emulsion was then dispersed into an aqueous solution of Tween 20 to generate a W/O/W ME composed of 80% of the primary emulsion, 10% of the solution in 40% Tween 20, and 10% water [72].

The droplet size of multiple emulsions (MEs) is notably larger in comparison to other nanodelivery systems, measuring approximately 1 μm with a zeta potential of −13 mV. In addition to the formulation, the authors conducted in vitro biological assays using the Erythrocyte-induced hemolysis in vitro method to evaluate the potential irritation of a novel topical preparation. Free Kojic Dipalmitate (KDP) led to the lysis of 4.09% ± 0.13% of erythrocyte membranes. KDP-unloaded MEs induced lysis of 1.57% ± 0.47% of erythrocyte membranes. The incorporation of KDP in ME resulted in 2.98% ± 1.12% lysis, demonstrating decreased erythrocyte lysis compared to free KDP. Therefore, all systems exhibited tolerable erythrocyte hemolysis [72].

The formulations, whether with or without the addition of KDP, underwent assessment for in vitro antioxidant activity over a 28-day period using the DPPH assay. Throughout the 28 days, there was a decline in the antioxidant power of all experimental groups, with the most significant decrease observed for free KDP. The differences between the samples were statistically significant ($p < 0.05$), and the observed lesser destabilization of the samples is likely attributed to the increased stabilization of the KDP-loaded ME formulation [72].

5. Conclusions

This article explores the development and use of Kojic Acid Dipalmitate (KDP) in skincare products, with a specific emphasis on its ability to hinder the production of melanin and its potential for treating disorders like melasma. KDP concentrations in skincare products often vary between 0.01% and 25% [81]. In 2018, Chandrashekar et al. conducted research that demonstrated that a combination cream including a 2% KDP formulation was both efficacious and safe for treating melasma [36,82].

The article explores the restricted number of patents associated with KDP, specifically focusing on one patent by Whittemore et al. (1998) for a cosmetic composition that lightens the skin and contains KDP [84]. Furthermore, the Shanghai Institute of Technology has a patent for Solid Lipid Nanoparticles (SLN) that include KDP, with the purpose of augmenting skin permeability and enhancing whitening effects [85,86]

The fundamental focus of this discussion is the use of nanotechnology in the formulation of KDP. Various preparations, including nanoemulsions, nanocreams, liposomes, and ethosomal suspensions, are explored in detail. The purpose of these formulations is to overcome the molecular weight restrictions of KDP and improve the capacity of the substance to pass through the skin, as well as its stability and effectiveness, while also minimizing any potential harmful effects.

The article highlights the importance of nanoemulsions in drug delivery systems for skin permeation, providing evidence from studies that demonstrates their efficacy in improving both the stability and activity of KDP on the skin. Nanoemulsions are favored because of their smaller particle sizes and lipophilic properties, which enable enhanced penetration and absorption of active ingredients into the skin.

In addition, the essay provides a comprehensive analysis of formulations such as nanocreams and liposomes, specifically examining their stability, particle sizes, and loading capacities. The focus is on the creation of ethosomal suspensions loaded with KDP, which show potential for effectively treating skin hyperpigmentation.

Ultimately, the study highlights the transformative influence of nanotechnology on the development of Kojic Acid Dipalmitate, augmenting its physical and chemical characteristics. The use of KDP in several nanoscale formulations has significant promise for enhancing effectiveness and skin advantages in cosmetic uses.

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