Advances in cosmeceutical nanotechnology for hyperpigmentation treatment

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Abstract Hyperpigmentation is a common and major skin problem that affects people of all skin types. Despite the availability of various depigmentation active ingredients for skin hyperpigmentation disorder, none of them are completely satisfactory due to their poor permeability through the skin layer and significant toxicity, thereby causing severe side effects such as irritative dermatitis, erythema, itching, and skin flaking. Nanotechnology plays an important role in advancing the cosmeceutical formulation by improving the solubility, stability, safety, loading efficiency, and dermal permeability of the active ingredients. The aim of this review is to offer a comprehensive discussion on the application of various nanomaterials in improving cosmeceutical formulations used to treat hyperpigmentation. Focus is placed on elucidating the advantages that nanotechnology can bring to some common hyperpigmentation active ingredients such as hydroquinone, arbutin, kojic acid, azelaic acid, and retinoic acid to improve their efficacy in treating hyperpigmentation.

Introduction

Over the past decades, technological advancements in cosmeceuticals are growing rapidly. The rise in the usage of cosmeceuticals in skincare can be attributed to an increase in consumer awareness of general skin health and physical esthetic attributes. Coupled with the rise of awareness of a healthy lifestyle, the role of cosmeceuticals and cosmetics has become essential in a person’s daily routine [1]. It is estimated that the rise in the market value and sales for the beauty and personal care market to go beyond $716 billion dollars by 2025 [1]. With such rapid development in skincare products, more quality and scientific assessments are needed to improve its efficiency.

Besides focusing on improving the efficacy of individual active agents, scientists have also been exploring more on how nanotechnology can improve the delivery and absorption of active ingredients to the skin [2, 3].
Nanotechnology has become a promising addition to the cosmetic industry due to its ability to enhance the properties of cosmetic products in general. Features such as absorption, texture, protection for active ingredients, and overall efficiency could all be manipulated and improved upon using nanotechnology [4]. Nanotechnology utilizes nanoparticles or nanomaterials which are naturally or synthetically derived ranging from 1 to 100 nm [5]. The nano-sized particles are able to impart numerous important properties in topical applications. Firstly, the minute size of nanoparticles allows for a high surface area to volume ratio which enables greater exposure of active molecules per dose administrated to the stratum corneum [6]. Secondly, nanoparticles are able to improve the absorption through the skin along with sustained release in order to increase blood circulation time of the encapsulated compound and improve the delivery of the active ingredients to the targeted site [7]. Besides, nanomaterials may also provide better stability of cosmeceutical compounds which may degrade due to oxidation or for other reasons [8]. Figure 1 showed the outline of the improvement of cosmeceutical compounds by nanoparticles.

Hyperpigmentation is one of the most notable skin maladies that is associated with discolorations or pigmentation problems [9]. Hormonal fluctuations, injury, skin inflammation, ultraviolet (UV) exposure, and improper medication are potential causes of hyperpigmentation [10]. These events can trigger an over-production of melanin by melanocytes within the skin layers which can result in dark spots or overall darkening of one’s skin tone [9]. Melanin is the natural pigment that gives our skin, eyes, and hair color, and is essential for the protection of human skin against radiation. However, an abnormal increase in melanin production can result in pigmentation disorders, such as ephelides, melasma, senile lentigines, and freckles [11]. Over the past decade, several classes of tyrosinase inhibitors such as phenolics, steroids, flavonoids, terpenes, oxadiazole, and bipiperidines have been reported to inhibit melanogenesis and enzymatic browning [12–14]. Brightening or anti-hyperpigmentation agents such as, arbutin, azelaic acid, kojic acid, and hydroquinone are commonly used in the market due to their ability to inhibit melanocytes or suppress melanin production [15–17]. However, these depigmentation agents hardly showed inhibitory activity towards tyrosinase in intact melanocytes. Some are even considered to be cytotoxic and unstable over time [17, 18]. With nanotechnology, the previously overlooked active ingredients could be further explored and formulated into more effective and safer depigmenting agents.

Although the use of nanotechnology in cosmeceuticals has been widely reported [4, 6, 19–21], specific details focusing on nanoparticles in improving the efficacy of depigmenting active ingredients have yet to be reviewed. Herein, we provide a general overview on the use of nanotechnology and the advantages it brings in improving the efficacy of anti-hyperpigmentation compounds. Specifically, this review revisits common depigmentation active ingredients such as hydroquinone, arbutin, kojic acid, azelaic acid, and retinoic acid and elucidates new approaches where nanotechnology could improve their efficacy in treating hyperpigmentation.

Nanoparticles in cosmeceuticals

The cosmeceutical industry uses various nanomaterials, from lipid nanostructures to metal-based nanocarriers, nanocrystals, and even polymer-based nanocarriers for various application (Fig. 2).

Recently, a variety of nanomaterials have been studied in different in vivo models with outstanding and promising outcomes [5]. Nanomaterials that are often studied alongside skin-based cosmetics can be divided into 2 main categories, namely organic nanoparticles and inorganic nanoparticles as shown in Fig. 2. Organic nanoparticles are mainly used in lipid and polymer-based nanocarriers. Inorganic nanoparticles are made up of metals and their oxides, and are generally water insoluble [1]. Organic nanoparticles are mainly used in the formulation of active ingredients by acting as carriers and absorption enhancers whereas inorganic nanoparticles are often used as bases for products that sit or act on the surface of the skin such as antimicrobial products or sunscreens. The main difference between the two lies with the sturdy nature of inorganic nanoparticles where their physical properties remain unchanged when applied topically [1]. Different classes of nanoparticles are further discussed below.

Organic nanoparticles

(1) Lipid and surfactant derived nanoparticles.

(a) Vesicular nanoparticles.

Lipid-based nanoparticles include vesicular nanoparticles such as niosomes and liposomes [1]. These vesicular nanocarriers are spherical, in-closed
vesicles that are made up of naturally self-assembling phospholipid bilayers or non-ionized synthetic amphiphilic lipids such as alkyl esters [6]. Liposomes range from 10 to 300 nm, which is comparatively larger than niosomes which range from 10 to 100 nm. These lipid-rich vesicles are able to enhance the penetration of encapsulated active ingredients due to their amphiphilic nature, which in turn boosts their bioavailability. Moreover, they are also biodegradable which is an environmental advantage.

(b) Non-vesicular nanoparticles.
Non-vesicular carriers including nanoemulsions, solid lipid nanoparticles (SLN) and nano-based lipid carriers (NLC) are mainly composed of differing heterogeneous systems that are dual-phased (aqueous and lipophilic) and stabilized with emulsifiers and surfactants (NLC). Nanoemulsions are dual-phase systems that contain oil in an aqueous medium and emulsifying agents [22]. Their ultrafine texture often leads to a silkier finish, enhancing product absorption as well as providing a boost in skin hydration [5]. On the other hand, SLNs and NLCs are made up of a lipid core containing either solidified lipids or liquidized lipids respectively. In general, both lipid nanocarriers can be used to deliver poorly water-soluble drugs and bioactive molecules [23]. Next, due to their inherent tuneable microstructure, they are also utilized as emulsion stabilizers [24].

(2) Polymeric nanoparticles.
Polymeric nanoparticles are categorized into nanocapsules and nanospheres. Nanocapsules are formed from a polymeric coating which shelters a liquid core that contains either an oil or surfactant that is loaded with the active ingredient whereas nanospheres are matrixes which trap the active ingredient within its network [6]. The main benefit that comes from the use of polymeric nanoparticles is their ability to encapsulate both hydrophilic and lipophilic active ingredients. Moreover, they can extend the lifespan of unstable compounds such as antioxidants and volatile chemicals such as fragrances [1]. Generally, polymeric nanoparticles can be prepared using synthetic or natural polymer. Polyethylene glycol, polylactides, and poly(lactic-co-glycolic acid) (PLGA) are examples of biodegradable synthetic polymers while poly(methyl methacrylate) and polyacrylates are few of the non-biodegradable synthetic polymer which are frequently used to deliver hydrophobic compounds in skin care formulations [25]. Chitosan, gelatin, and albumin are natural polymers that are biodegradable and

![Diagram](image-url)
biocompatible. Chitosan is commonly used natural polymer because it possesses great potential for surface modification [26] and is suitable for encapsulating negatively charged compounds which can help in cellular internalization [25]. In comparison, synthetic polymers are more flexible as they were able to turn into various shapes and size compared to natural polymer [27].

(3) Nanocrystals.
Nanocrystal is another form of polymeric nanoparticles that are mainly used for the delivery of insoluble active ingredients [22]. Nanocrystals possess a large surface area which aids the absorption of otherwise insoluble active ingredients. Recently, Hiranphinyophat and co-workers reported a poly(2-isopropoxy-2-oxo-1,3,2-dioxaphospholane) (PIPP) modified cellulose nanocrystal as a vehicle for topical delivery of lipophilic compounds. The results indicated that the surface modified nanocrystal could increase surface hydrophobicity, emulsifying efficiency, stability, as well as penetration depth through all skin layers with increasing drug accumulation [28].

Inorganic nanoparticles

Inorganic nanoparticles are commonly used as active substances, nanocarriers, and modifiers in cosmetic products. Carbon-based nanotube, nanorod, noble metals, metal oxides, and mesoporous nanostructures are several classes of inorganic nanoparticles used in commercial cosmetic products. Carbon-based nanotubes are widely used for coloring hair, eyelashes, and eyebrows due to its high resistance to various
shampoos and its heat dissipation abilities [29, 30]. Mesoporous silica is a porous form of silica composed of hexagonal array of nanoscale pores which can accommodate the active compounds and control its release [31]. Mesoporous silica encapsulated with octal methoxycinnamate (MCX) and benzophenone-3 (BZP) were reported to improve UV protection compared to the non-encapsulated-free compounds alone. [32, 33]. Apart from mesoporous silica, inorganic oxides nanoparticles such as TiO₂, ZnO, CeO₂, and ZrO₂ are able to scatter and reflect UV radiations. Due to this property, they are widely included in the formulation of cosmetic sunscreen [34].

Advantages and drawbacks of nanomaterials used in cosmeceutical formulation

Based on the nanomaterials discussed, the advantages and disadvantages will be highlighted further specifically for organic nanoparticles and inorganic nanoparticles in Table 1.

Topical depigmenting agents

Skin-lightening compounds, such as hydroquinone, kojic acid, arbutin, azelaic acid, and retinoic acid, are often used to treat hyperpigmentation disorder. The mode of action of depigmentation agents can be classified as follows: (i) inhibition of tyrosinase; (ii) inhibition of melanosome transfer; (iii) scavenge active oxygen and limiting oxidative damage to cell membrane structure; and (iv) interaction with copper which normally serve as a catalyst in the formation of pigment [35]. Table 2 shows the classification of the depigmenting agents based on their mechanism of action.

However, these depigmenting compounds are associated with many adverse effects such as irritative dermatitis, erythema, itching, and skin flaking due to their poor solubility, poor permeability through the stratum corneum, as well as high toxicity [48]. The poor skin permeability of depigmenting compounds is often the result of the overaccumulation of the active ingredients and increment of skin retention period which in turn escalates the likelihood of adverse effects mentioned above [49, 50]. Table 3 depicts clinical studies on various topical depigmenting agents and their observed side effects.

Overall, these depigmenting compounds exhibit good efficacy. However, the severe side effects prevented these depigmenting agents from being used in numerous countries. Several studies have shown that the encapsulation of depigmenting compound in nanoparticles could reduce its adverse effects, promotes target delivery, and enhance its stability [60–64]. The advantages on the use of nanotechnology in various depigmenting compounds are deliberated below.

Application of nanoparticles in depigmentation compounds

Studies on hydroquinone loaded nanoparticles

Hydroquinone (Fig. 3) is often used in the production of skin-lightening products as it functions to inhibit tyrosinase activity [65]. It is a known irritant whereby its side effects include skin irritation and erythema [66]. In cosmetic applications, hydroquinone suffers from instability due to rapid oxidation, insufficient skin penetration because of its hydrophilic structure, and encounter serious side effects due to systemic absorption. Several studies were aimed to load hydroquinone into nanoparticles to overcome the mentioned drawbacks of depigmenting agents.

Studies have shown that encapsulation of hydroquinone in lipid nanoparticles were able to enhance the stability against oxidation and possess better skin penetration ability compared to the hydroquinone [60]. An in vitro rat skin penetration study showed approximately threefold higher drug accumulation and 6.5-fold lower drug entrance into receptor phase of Franz cell confirming the lower systemic absorption of drug using hydroquinone loaded SLN compared with hydroquinone hydrogel. The lipoid nature of SLN colloidal carrier is likely to enable penetrated drugs to localize in the skin. This may reduce toxic side effects as systemic absorption is minimized. Moreover, another research group has also reported a better skin penetration and enhanced protection towards UVA/UVB irradiation using hydroquinone in nanostructured lipid carrier (NLC) compared to hydroquinone alone [67]. In their in vitro artificial skin permeation study showed that percutaneous penetration ability of hydroquinone encapsulated in NLC was significantly greater than hydroquinone only.
In addition, it has been revealed that hydroquinone after loaded in cellulose nanocrystals are exhibited sustained release manners and showed stability against oxidation [68]. The study showed a sustained release profile of hydroquinone (80% of bound hydroquinone released in 4 h) which improved the efficacy

| Table 1 | Advantages and disadvantages of organic and inorganic nanoparticles in treating hyperpigmentation [19, 35–43] |
|----------|------------------------------------------------------------------------------------------------------------------|
| **Organic nanoparticles** | **Advantages** | **Drawbacks** |
| Niosomes | - Allows for controlled and targeted compound delivery | - Chance for leaking and hydrolysis of entrapped compound and reducing shelf life |
| | - Increased dermal penetration | - Physically unstable |
| | - Low toxicity, biocompatible and nonimmunogenic | - Tends to aggregate |
| Liposomes | - Increased stability for encapsulated compound | - High production cost |
| | - Biocompatible and biodegradable | - Low solubility |
| | - Increased efficacy of encapsulated active ingredient | - Chance for leaking of entrapped active ingredient |
| Nanostructured lipid carrier (NLC) | - Physically stable | - Irritative and sensitizing actions caused by some surfactant that use to produce NLC |
| | - Higher loading capacity compared to SNL | - Insufficient studies in the preparation of NLCs |
| | - Extended release of drug | |
| Liposomes | - Increased stability for encapsulated compound | |
| | - Biocompatible and biodegradable | |
| | - Increased efficacy of encapsulated active ingredient | |

| **Table 2** | Classification of depigmenting agents based on their mechanism of action [44–47] |
|----------------|------------------------------------------------------------------------------------------------------------------|
| **Mechanism of action** | **Depigmenting compounds** |
| i) Inhibition of tyrosinase | Hydroquinone, azelaic acid, kojic acid, and arbutin |
| ii) Inhibition of melanosome transfer | Retinoids (including of retinoic acid) |
| iii) Reactive oxygen species scavengers during melanin synthesis | Ascorbic acid |
| iv) Interaction with copper | Kojic acid, ascorbic acid |
and simultaneously reduced the adverse effects of hydroquinone.

All of the above examples showed that nanotechnology is a promising approach for topical administration of hydroquinone to overcome hyperpigmentation with a suitable skin penetration and low systemic absorption to reduce the adverse effects of hydroquinone.

Studies on arbutin loaded nanoparticles

Arbutin (Fig. 4) is commonly used as a skin-lightening and brightening agent in skincare and cosmetic products [69]. The main mode of action for arbutin is inhibit the synthesis of melanin by acting as a tyrosinase inhibitor [70]. Besides, it is also

![Chemical structure of hydroquinone](image-url)
possesses anti-inflammatory and antioxidant properties [71]. It is highly hydrophilic and hygroscopic due to its chemical structure which contains multiple hydroxyl groups. Therefore, it usually suffers from poor absorption and penetrance through the stratum corneum [72]. The high lipid content of the skin renders arbutin difficult to permeate through it and diffuse into the inner cells. A recent study indicated that the arbutin’s adverse effects is triggered by external production of hydroquinone due to exposure of ultraviolet rays and skins microorganisms [66].

One of the methods to mitigate the poor penetration is by loading arbutin into chitosan polymeric nanoparticles. Chitosan is a biodegradable polymer made from de-acetylated chitin that possesses high biocompatibility, non-toxic, and can interact with a large variety of polyanions [73]. When it is made into a nanocarrier, positively charged chitosan nanoparticles (CNP) was able to increase permeation through the skin due to the increased interaction with negatively charged cellular surfaces and eventual uptake into melanocytes via endocytosis or phagocytosis [74]. Ayumi et al. reported that the α-arbutin and β-arbutin chitosan nanoparticles demonstrated prolonged rate of absorption by releasing the active compound slowly over a sustained 52-h period [74].

Gold nanoparticles (GNPs) have become prevalent within the cosmeceutical industry due to their inert and non-toxic nature. Park et al. described a novel arbutin-GNP nanocomplex which possesses superior brightening properties compared to arbutin alone [75]. In their study, they measure the melanin content from both the tested melanocytes (intercellular melanin) and their culture medium (extracellular melanin), arbutin-GNP nanocomplex were able to inhibit the production of intracellular and extracellular melanin of up to 22.7 and 47.7% respectively versus 21.8% and 31.8% with arbutin alone. The study also reveals that arbutin-GNP nanocomplex exhibited better anti-inflammatory activity and lower toxicity comparing to pure arbutin.

Guar gum (GG)-based nanomaterials have been extensively used for skin and percutaneous administration to controlled release and delivery enhancement [76–78]. A cross-linked amphiphilic GG nanocarriers loaded with arbutin was reported [79]. Through the modification of guar gum with hydrophobic short-chain alkylglycerol, namely glycidol butyl ether (GBE), the GBE-GG nanocomplex loaded with arbutin imparted a higher degree of hydrophobicity which increases its permeation through the stratum corneum. Besides, the results suggested the absence of cellular toxicity and better cellular uptake across the cultured human keratinocyte HaCaT cells that increase the biological membrane permeability, suggesting their potential as safe nanocarriers for topical delivery.

Nanoemulsion of arbutin loaded with coumaric acid has also been showed to improve the delivery and stability of arbutin [61]. Through the use of multi-phase (w/o/w) nanoemulsion, it was found that the encapsulated arbutin achieved high stability and high encapsulation efficiency using a hydrocolloid medium. Furthermore, the encapsulated arbutin was able to exhibit sustained release (86%) due to the nature of the gelatin hydrocolloid in compared to free

**Fig. 4** Chemical structure of arbutin
form of arbutin, which only resulted in a 5% overall release over a period of 6 h.

In conclusion, the application of different types of nanotechnology has been able to overcome the weak permeating capability of arbutin by either encapsulating it via polymeric nanocarriers, complexing it with inorganic nanoparticles such as GNPs or formulating it within a nanoemulsion.

Studies on azelaic acid–loaded nanoparticles

The main use of azelaic acid (Fig. 5) originates from its antibacterial, anti-inflammatory, and skin brightening properties [80]. Its ability to treat hyperpigmentation lies with its nature as a potent reversible inhibitor of the tyrosinase enzyme [81]. As azelaic acid possess two carboxyl groups, it is easily ionized. The ionized compounds tend to exhibit poorer skin permeability due to the hydrophobic nature of the skin [82, 83]. Thus, in response to azelaic acid’s poor permeability through the skin, azelaic acid encapsulated by nanoparticles were able to increase absorption to exhibit significant therapeutic effect [82].

Nanocrystals have received considerable attention in cosmeceutical as they increased compound’s solubility, dissolution rate, and increased adhesion properties of nanocrystal to the skin [84, 85]. With the aims to enhance the solubility and stability of azelaic acid, Tomic and co-workers reported the encapsulation of azelaic acid in nanocrystals suspended in Pluronic® F127 and hyaluronic acid (PHA). These azelaic acid nanocrystals showed improved aqueous solubility and dissolution rate [62]. The results suggested that the nanocrystal of azelaic acid and its incorporation in PHA hydrogel gave better skin bioavailability in comparison to an azelaic acid–containing standard commercial product.

It has also been revealed that azelaic acid loaded in nanoemulsion with hyaluronic acid exhibited better drug retention and tyrosinase inhibition activity [86]. In their study, hyaluronic acid was used to formulate into nanoemulsion along with azelaic acid because hyaluronic acid was previously reported to significantly decrease the melanin synthesis due to improving the interaction of nanoemulsion and melanocytes [87]. At last, with the help of nanotechnology and hyaluronic acid, azelaic acid–loaded nanoemulsion showed lesser tyrosinase activity and permeated through the skin without showing cytotoxic activity.

A study showed that the use of nanostructured lipid carriers (NLC) loaded with azelaic acid allowed for its enhancement towards its targeting sites such as melanocytes. This is due to their small particle size and its innate occlusive effect that allows for better penetration through the stratum corneum [88]. When tested for their permeation capabilities, the release rates of azelaic acid-NLC, azelaic acid gel, and azelaic acid in water was found to be 21%, 38%, and 78% respectively. Despite the slower release rates, azelaic acid-NLC exhibited a higher initial burst release of up to 5%. The azelaic acid-NLC’s ability for sustained release and high initial burst release is advantageous for topical application as it allows for a rapid onset of action and allows for a depot effect to take place in a localized area. The slower release of azelaic acid-NLC also mitigated the occurrence of side effects as the skin was not exposed to high amounts of azelaic acid over a period of time compared to azelaic acid gel and azelaic acid in water.

In short, the use of nanotechnology is able ameliorate the drawbacks faced when formulating azelaic acid such as its poor aqueous solubility and occurrence of dermal adverse effects. Examples including nanoemulsions and nanocrystals allow better solubility of azelaic acid and with the use of NLCs; the likelihood of adverse effects is lowered due to the gradual release effect of azelaic acid–loaded NLC formulation.
Studies on kojic acid–loaded nanoparticles

Kojic acid (Fig. 6) primarily functions as a skin-lightening agent by acting as an inhibitor for tyrosinase [89]. The main mode of action for kojic acid as an inhibitor is through its ability to chelate to the copper within the enzymes active site [90]. It is highly hydrophilic as its chemical structure containing of two hydroxyl group. The hydrophilic nature of the compound makes it difficult for kojic acid to penetrate through the stratum corneum and hindered the accumulate of kojic acid in the target sites [18, 91]. Several studies have reported the concern of kojic acid regarding its toxicity [92], carcinogenicity, mutagenicity [93], irritancy [94], hepatocarcinogenicity [95, 96], genotoxicity [97], and tumor-initiating activity [98]. Loading kojic acid in nanoparticle has been envisage to counteract these adverse effects.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been extensively studied as way to bypass the hydrophilic nature of kojic acid. Khezri et al. reported a kojic acid–loaded SLNs optimized by some lipid excipients and surfactants in order to increase its loading. The results indicated that the kojic acid-SLNs dispersion can increase the dermal delivery of kojic acid with higher concentration, better controlled release, and more tyrosinase inhibition potency compare with the free form of kojic acid [99]. Recently, Khezri et al. reported the formulation of kojic acid loaded in NLCs were showed to have better release profile, and more potent tyrosinase inhibitory as well as antioxidant activities compared to the pure kojic acid [63]. Results of these studies indicated that kojic acid-SLNs and kojic acid-NLCs with lipid excipients and surfactant increase skin permeation. This implies the potential of nanotechnology for kojic acid delivery in topical application.

A very recent study on different formulations of oil-in-water (O/W) kojic acid nanoemulsion for topical application [100]. The study revealed various parameters to generate kinetically stable nanoemulsion at a recommended pH range of pH 4.95 to 5.18 for 6 weeks storage. The results suggested the suitability of the kojic acid emulsion for topical application.

The above studies revealed that the loading of kojic acid in nanoparticles are able to reduce the hydrophilic nature of kojic acid and thereby increase its skin permeation and stability, by either loaded kojic acid with SLNs and NLCs or formulating it into nanoemulsion.

Studies on retinoic acid–loaded nanoparticles

Retinoic acid (tretinoin; Fig. 7) is a metabolite of vitamin A [101]. It is often used in the treatment of melasmas and other pigmentation disorders [58]. When used topically, it functions to increase the pigment
transfer to keratinocytes, as well as the rate at which skin cells are shed. It is also known to inhibit the production of tyrosinase [102]. Further benefits from retinoic acid also include their superior antioxidant and antimicrobial capabilities. The use of retinoic acid in product formulation is often met with challenges due to its inherent lipophilicity, which results in poor aqueous solubility. This limits its ability to be formulated in aqueous mediums and often results in the use of harmful co-solvents such as ethanol and propylene glycol [103]. Furthermore, the unstable nature of retinoic acid has also led to a drop in its therapeutic efficacy. This is due to increased liability and decreased stability when exposed to light, heat, oxidation, and changes to environmental pH [104, 105].

Ourique et al. (2011) describe the use of a lipid-core polymeric nanocapsules (LCNC) to encapsulate retinoic acid in order to increase the photostability and improve skin retention time. When tested for half-life and effects of photodegradation, the retinoic acid-LCNC achieved a $t_{1/2}$ of 26.6 h compared to marketed gel containing retinoid acid which has a $t_{1/2}$ of 3.8 h. Furthermore, the rate of degradation was significantly reduced in retinoic acid-LCNC compared to retinoic acid, from 68.64 to 24.17% [103].

Vesicular nanocarriers such as liposomes have also been documented to aid retinoic acid to retain on the skin. It also offers enhanced protection from UV radiation. Furthermore, the use of phospholipids in the creation of such nanocarriers offers a higher biocompatibility compared to traditional mediums such as gels and creams, increasing retinoic acid’s therapeutic efficacy. A study by Raza et al. demonstrated the use of SLNs, NLCs, and liposomes to enhance the drug delivery of retinoic acid. The reported study indicates that nanoparticulate carriers could enhance the photostability, skin transport, and anti-psoriatic activity of retinoic acid, which proved to be more effective and biocompatible than the marketed product [64].

A study by Shah et al. (2007) showed improved physical stability and dermal tolerability of retinoic acid with encapsulation of SLNs [106]. When tested for photodegradability, retinoic acid-SLNs proved to be superior when irradiated, retaining up to 71% of the retinoic acid content in comparison to retinoic acid in methanol which only retained 12%. The irritating properties of retinoic acid has been stated to originate from its acidic functionality (carboxyl group) when it is contact with the skin. This problem can be possibly be overcome using retinoic acid-SLN, whereas Draize patch test on rabbits attained a lower irritation score compared to the marketed retinoic acid formulation.

In summary, the studies above suggesting the emerging of nanotechnology in retinoic acid able to eliminate the drawbacks such as its poor aqueous solubility and photosensitivity.

**Trends of patents and research papers on nanotechnology in hyperpigmentation treatment**

In order to further study on the relevance and commercial research of nanomaterials for the improvement to the delivery and efficacy of the aforementioned depigmenting compounds (hydroquinone, arbutin, azelaic acid, kojic acid, and retinoic acid), a total of 44 patents and articles on the encapsulation of the active ingredients by nanoparticles were filed to date. Based on Fig. 8, only two patents and one paper were published prior to 2010 compared to 44 publications from 2010 to 2021. The rapid rise in the number of patents and papers can be attributed to the exponential growth in the cosmetics industry. This provides opportunities to expand and investigate on...
the use of nanocarriers in the formulation of the five mentioned active ingredients. Among the depigmenting agents, arbutin remains to be the most studied active ingredient in conjunction with nanotechnology. The extensive study of arbutin can be attributed by its higher skin tolerance and reduced side effects compared to traditional skin brightening agents such as hydroquinone, retinoic acid, and kojic acid [66, 107].

Nanotechnology-based cosmeceuticals continually gain attention over the past few decades. According to the market analysis by the Woodrow Wilson International Centre on Emerging Nanotechnology, 788 out of more than 1600 products were marketed as nanotechnology products for cosmetic [108]. The European Union (EU) revamped cosmetic regulation (Directive 76/768/EEC) in 2009 under a new name, EC Regulation 1223/2009 [109], which included international guidelines in order to address issues in the technological insufficiencies within the cosmetic industry and to include recent research developments towards formulating new nano-based cosmetics [110]. This gave the push towards the usage of research data in developing more sophisticated nano-based products, increased transparency when providing information towards customers, and rigorous safety testing, especially within the EU countries. Notably, these guidelines only apply to nanomaterials that are synthetic, insoluble, or not readily biodegradable such as metals. Consequently, materials that are soluble and biodegradable such as lipid-based nanoparticles (liposomes, NLC, and SLN) are not considered as nanomaterials under the EC Regulation 1223/2009, which allowed for several industries including the cosmetic industry to utilize these nanomaterials more extensively as they are not directly regulated by the EC regulation and can be more freely studied and marketed. In summary, increased cosmetic interest, government backing as well as decreased regulation for certain types of nanomaterials has led to an overall increase in both patents and research towards the use of nanotechnology for cosmetic products.

Based on the patents and research papers studied, it was found that a vast majority of the discussed papers researched on the use of lipid nanoparticles as nanocarriers in improving the efficacy of the depigmenting active ingredients (14 out of the 25 listed papers). In comparison, the least studied nanocarrier was found to be inorganic nanoparticles which only had 1 paper associated with treatment of depigmenting agents based on Table 4.

The rise in the popularity of lipid nanoparticles in research is due to several important properties such as high skin penetration ability, safe for topical application,
biocompatible, and biodegradable when used topically [119–121]. Further studies have also shown that the SLNs and NLCs can act as a physical ultraviolet ray blocker [22, 119]. This allows for the encapsulation of photosensitive materials such as retinoic acid. Unlike lipid nanoparticles, inorganic nanoparticles such as gold, titanium, and silica-based nanoparticles are considered to be insoluble particles [1]. Thus, these materials are unlikely to degrade after topical application [122]. Moreover, there is high risk in utilizing these inorganic nanoparticles as they may have risks in terms of occupational, environmental, or even toxicity [123]. Furthermore, inorganic nanoparticles were more likely to use as active agents for UV protection rather than acting as nanocarriers for other active ingredients [1].

**Conclusion**

Nanotechnology has recently received increased attention in cosmetic industry. Some advances have been widely applied such as in formulations for skin whitening but treating hyperpigmentation has often been overlooked. In this review, we have summarized how the current nanotechnology helps in solving the problem of depigmentation agents, in particular: improving the solubility; enhancing the stability; reducing its toxicity by controlling the release of active ingredient; and increasing its entrapment efficiency and dermal penetration of the active ingredient to reach the stratum corneum. From the 44 reported patents and articles, lipid nanoparticles were found to be the most widely used nanocarriers in treating hyperpigmentation as they may have high skin permeability, biocompatible, and biodegradable [119–121]. This allows for the encapsulation of photosensitive materials such as retinoic acid. Unlike lipid nanoparticles, inorganic nanoparticles such as gold, titanium, and silica-based nanoparticles are considered to be insoluble particles [1]. Thus, these materials are unlikely to degrade after topical application [122]. Furthermore, inorganic nanoparticles were more likely to use as active agents for UV protection rather than acting as nanocarriers for other active ingredients [1].

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**Author contribution**

MJT: conceptualization, literature search, writing, and editing manuscript; YKC: conceptualization, literature search, writing, and editing manuscript; KYY: conceptualization, reviewing, and editing manuscript.

**Table 4** List of nanocarriers from research papers that utilized the five depigmenting agents

|                      | Hydroquinone | Arbutin | Azelaic acid | Kojic acid | Retinoic acid |
|----------------------|--------------|---------|--------------|------------|---------------|
| Lipid nanoparticles  | SLN          | Ghanbarzadeh et al. [60] | -           | -          | Khezri et al. [99]; Mohammadi et al. [111]; Raza et al. [64]; Shah et al. [106]; Boskabadi et al. [112] |
|                      | NLC          | Wu et al. [67] | -           | -          | Khezri et al. [63]; Raza et al. [64]; Asfour et al. [115] |
|                      | Niosomes     | -       | -           | -          | Wu et al. [67] |
|                      | Liposomes    | -       | -           | -          | -             |
|                      | Chitosan     | -       | Radma et al. [116] | -          | -             |
|                      | Biodegradable polymer | - | - | Reis et al. [117] | - |
|                      | Silica       | -       | -           | -          | Lima et al. [118] |
|                      | Guar gum     | -       | -           | -          | -             |
|                      | Nanoemulsion | -       | Huang et al. [61] | - | Yun et al. [100] |
|                      | Nanocrystal  | -       | Jacobus Berlitz et al. [86] | - | - |
|                      | Inorganic nanoparticles | Gold | - | Park et al. [78] | - |

**Table 4** List of nanocarriers from research papers that utilized the five depigmenting agents.
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