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Review Article

Molecular Mechanisms of Melanogenesis in Hyperpigmentation: From Signaling Pathways to Nanocarrier-Based Therapeutic Strategies

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Abstract: Hyperpigmentation remains a complex dermatological challenge, often resistant to conventional topical therapies due to the skin's inherent barrier function and the chemical instability of active depigmenting agents. Traditional formulations of depigmentation agents frequently suffer from poor dermal penetration and dose-dependent toxicity, leading to localized irritation and high relapse rates. This review highlights the transformative role of cosmeceutical nanotechnology in overcoming these limitations through advanced delivery systems, including lipid-based nanocarriers, polymeric nanoparticles, and microbiota-derived metabolite platforms. These nanosystems enhance the stability, controlled release, and targeted delivery of active compounds to melanocytes within the basal epidermis while modulating key molecular pathways involved in melanogenesis. Their mechanisms include inhibition of tyrosinase activity through active-site copper chelation, suppression of microphthalmia-associated transcription factor (MITF) signaling, and disruption of melanosome transport and transfer to keratinocytes. Emerging microbiota-based approaches further contribute by regulating oxidative stress, inflammation, and pigmentation while helping maintain skin homeostasis. Experimental and clinical evidence demonstrates that nanocosmeceutical formulations significantly improve depigmenting efficacy. Despite these advantages, challenges remain regarding nanotoxicity, long-term safety, large-scale manufacturing, and the lack of harmonized regulatory frameworks governing nanocosmeceuticals. As demand for effective and minimally invasive skincare continues to grow, nanotechnology provides a promising strategy for developing safer, more stable, and highly bioavailable therapies for hyperpigmentation. Continued research, standardized safety evaluation, and clearer regulatory guidelines are essential to facilitate the successful clinical translation and commercialization of nanotechnology-based depigmenting formulations.

Keywords: Melanogenesis, Tyrosinase inhibition, Nanotechnology, Molecular targeting, MITF pathway

1. Introduction

Hyperpigmentation is a common dermatological condition characterized by localized or generalized darkening of the skin that arises from excessive production and deposition of melanin in the epidermis or dermis layer [1]. This physiological process is primarily driven by the activation of melanocytes due to ultraviolet (UV) exposure, hormonal imbalance, inflammation or side effects of medications [2]. It can be further categorised into four types of clinical manifestations which are melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, and ephelides [3].

At the molecular level, these diverse etiological triggers converge on complex intracellular signaling pathways within melanocyte. For instance, UV radiation prompts neighboring keratinocytes to release α-melanocyte stimulating hormones (α-MSH) and

adrenocorticotropic hormone (ACTH), which bind to the melanocortin 1 receptor (MC1R) on the melanocyte membrane. This binding will activate the cascade signaling and thus downregulate the MITF. MITF coordinates the tyrosinase, tyrosinase-related protein 1 (TYR1) and tyrosinase-related protein 2 (TYR2) [4]. These enzymes catalyze the rate-limiting steps of synthesizing eumelanin and pheomelanin within melanosomes before they are transferred to keratinocytes. Besides, recent studies revealed that hyperpigmentation can be modulated by skin microbiome and local inflammatory cascade. Commensal skin microbiota like *Cutibacterium acnes* and *Staphylococcus epidermidis,* play a role in maintaining the epidermal homeostasis and modulating the innate immunity [5]. Disruption of these microbiomes could lead to release of inflammatory cytokines that upregulate melanogenesis.

The prevalence of hyperpigmentation is notable, affecting a portion of the global population yet it is more common and more distressing in people with darker skin phototype such as Fitzpatrick scales IV–VI [6]. For example, melasma is estimated to affect approximately half the pregnancy population and is a leading cause of dermatological consultation in Hispanic and Asian populations. Similarly, PIH is an almost universal consequence of any inflammatory dermatosis like acne or eczema [6]. The impact of these conditions could lead to psychosocial distress which reflects on individuals who report decrease in self-esteem and diminish quality of life [7]. Current treatment strategies for hyperpigmentation involved topical agents, chemical peels and laser therapy. The first line treatment typically using the topical depigmentation agents that works through various mechanisms to reduce the melanin count [7]. Though it is convenience options for almost everyone, some treatment associated with significant side effects such as hydroquinone, when applied in long term or high amount could have irritation and exogenous ochronosis [2]. Other agents may also have skin delivery challenges such as poor penetration, inadequate stability or limited efficacy as monotherapies [8]. Therefore, to overcome these challenges, exploring advanced delivery systems to enhance the efficacy and safety of anti-pigmentation agents is necessary. Nanotechnology offers potential advantages such as improving stability of the depigmentation compounds and enhancing skin penetration to basal layer where melanocytes reside. By bridging the gap between cosmetic appeal and pharmaceutical efficacy, nanotechnology-based formulations represent the next frontier in the precise and sustainable management of hyperpigmentation. While previous literature has documented the individual efficacy of various depigmentation agents, there remains a critical need for comparative evaluation of how specific nanotechnology-based delivery systems could overcome the current limitations in conventional topical dosage forms.

The purpose of this review is to investigate the roles of nanotechnology in improving the safety and efficacy of anti-pigmentation agents. This review highlights the application of nanocarriers like lipid-based systems and polymeric nanoparticles in enhancing the stability, skin penetration, and controlled release of anti-pigmentation agents. Hence, this review provides comparison of different nanotechnology-based and advanced delivery systems to determine their suitability for specific therapeutic challenges. Furthermore, this review discusses the therapeutic potential, recent development from 2022 to 2025, and difficulties related to clinical and cosmeceutical development of nanotechnology-driven methods for controlling hyperpigmentation. By integrating these molecular and microbiological perspectives with nanotechnology-based therapeutic strategies, this review aims to provide a holistic framework for next-generation dermatological inventions.

1.1. Review Methodology

This review employed a systematic literature search using various databases such as SCOPUS, PubMed, MDPI, Web of Science, and Google Scholar. to identify relevant publications. Keyword combinations such as "nanotechnology AND hyperpigmentation" and "Nanocarrier AND hyperpigmentation" were used to retrieve articles focused on advanced drug delivery systems. The search was limited to publications from 2010 to 2025 to encompass both historical developments and recent advances. Figure 1 both topics exhibit a clear upward trend in publication volume over 15-year period. From 2010 to 2022, the number of publications grew gradually, followed by a phase of moderate growth from 2022 to 2025. A notably search was observed from 2019 onwards, heightened research interest and increased innovation in the field. The data strongly indicate that scientific attention toward nanotechnology in hyperpigmentation has accelerated significantly, particularly over the last decade. This trend suggests a sustained and growing emphasis on these technologies, likely driven by ongoing advancements in biotechnology, personalized medicine, and cosmeceutical innovation.

Studies were selected based on predefined inclusion and exclusion criteria. The inclusion criteria were:

1. Original research articles or review papers published in peer-reviewed journals;
2. Written in English;
3. Studies investigating nanotechnology-based systems for hyperpigmentation treatment, prevention, or diagnosis;
4. Studies involving nanocarriers such as nanoparticles, liposomes, nanoemulsions, nanostructured lipid carriers, polymeric micelles, dendrimers, or related nanosystems;

5. Studies reporting outcomes related to drug delivery efficiency, skin penetration, therapeutic efficacy, safety, stability, or formulation optimization.

The exclusion criteria were:

1. Conference abstracts, editorials, letters, patents, book chapters, and non-peer-reviewed publications;
2. Non-English publications;
3. Studies unrelated to hyperpigmentation or pigmentary disorders;
4. Studies focusing solely on conventional formulations without nanotechnology components;
5. Duplicate records or articles lacking sufficient methodological details or relevant outcome data.

The screening process involved the removal of duplicate records, followed by title and abstract screening to assess relevance. Potentially eligible articles were subsequently subjected to full-text evaluation. Only studies fulfilling all eligibility criteria were included for qualitative synthesis. Data extracted from selected studies included nanocarrier type, active ingredients, particle size, formulation characteristics, skin penetration performance, therapeutic outcomes, and safety profiles.

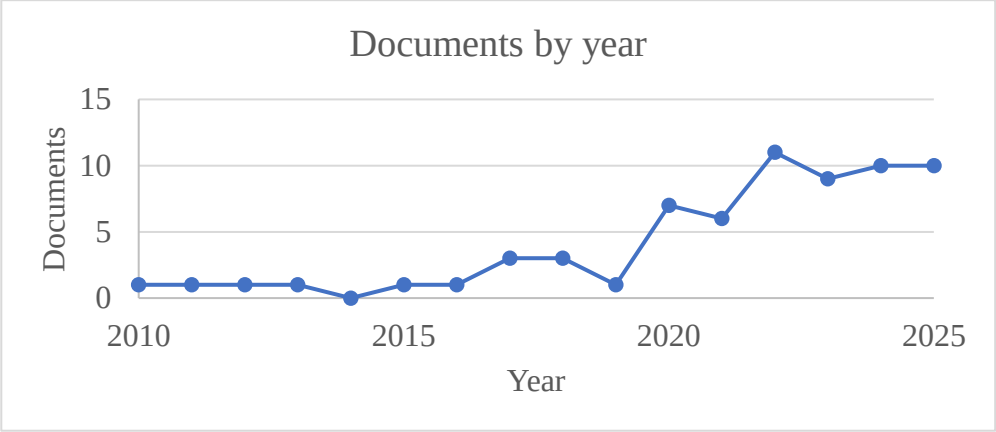

Figure 1. Numbers of documents with related keywords of "Nanotechnology AND hyperpigmentation" and "Nanocarrier AND hyperpigmentation" published from 2010 to 2025 according to SCOPUS (Image generated through excel).

2. Pathophysiology of Hyperpigmentation

Melanin is distributed throughout the skin, hair, eye and other tissues and it plays a role in maintaining skin homeostasis and photoprotection. Melanogenesis takes place within a functional anatomical structure known as the epidermal-melanocyte units. Melanin is not synthesized freely within the cytoplasm but instead it is synthesized and stored in the

membrane bound, lysosome-like organelles called melanosomes [9]. This compartmentalization is essential to shield the host cell from the highly reactive cytotoxic quinone intermediates generated during biosynthesis pathway. Melanogenesis begins with the oxidation of L-tyrosine to DOPAquinone by monophenolase activity of tyrosinase or oxidation of DOPA to DOPAquinone by diphenolase activity of tyrosinase [10]. Firstly, DOPAquinone reacts with cysteine to produce 5-S-cysteinylDOPA and 2-S-cysteinylDOPA that can later enter the pheomelanin synthesis pathway. These two chemical compounds will be oxidised into quinones and produce intermediates such as benzothiazole and benzothiazine by intramolecular cyclization. Both intermediates produced in the intramolecular cyclization are used as building blocks to synthesize the reddish-yellow polymer pheomelanin [10]. Besides, oxidation of DOPAquinone into DOPAchrome via leukoDOPAchrome will enter the eumelanin synthesis pathway. Later, DOPAchrome is converted into 5,6-dihydroxyindole-2-carboxylic acid (DHICA) by DOPAchrome tautomerase activity of TYRP-2 or to 5,6-dihydroxyindole (DHI) by releasing carbon dioxide. Lastly, building blocks of brownish-black eumelanin polymers, quinones, are produced through oxidation of DHI by 2 enzymatic activities like DHICA oxidase activity of TYRP-1 and DHI oxidase activity of tyrosinase [9]. Overproduction of quinones leads to accumulation of brownish-black eumelanin and therefore hyperpigmentation occurs. There are five main leading factors causes hyperpigmentation which are UV exposure, genetic predisposition, inflammation, hormonal imbalance and medications used [11]. The pathway of melanin synthesis is presented in Figure 2.

Beyond the classical melanogenic pathway, recent studies have identified several regulatory mechanisms that contribute to melanocyte homeostasis and pathological hyperpigmentation. One of the most important pathways is the Wnt/β-catenin signalling pathway, which plays a critical role in melanocyte stem cell maintenance, differentiation, and regeneration. Canonical Wnt ligands bind to Frizzled receptors and low-density lipoprotein receptor-related proteins (LRP5/6), resulting in stabilization and nuclear translocation of β-catenin [11]. Nuclear β-catenin subsequently interacts with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors to promote the expression of MITF, thereby enhancing melanocyte proliferation, differentiation, and melanogenesis. Dysregulation of Wnt/β-catenin signalling has been implicated in persistent pigmentary disorders by promoting excessive melanocyte activation and prolonged melanogenic responses following UV exposure or tissue injury. Crosstalk between Wnt signalling and the cAMP/PKA pathway further amplifies MITF expression, making this pathway an emerging molecular target for anti-hyperpigmentation therapies [11,12].

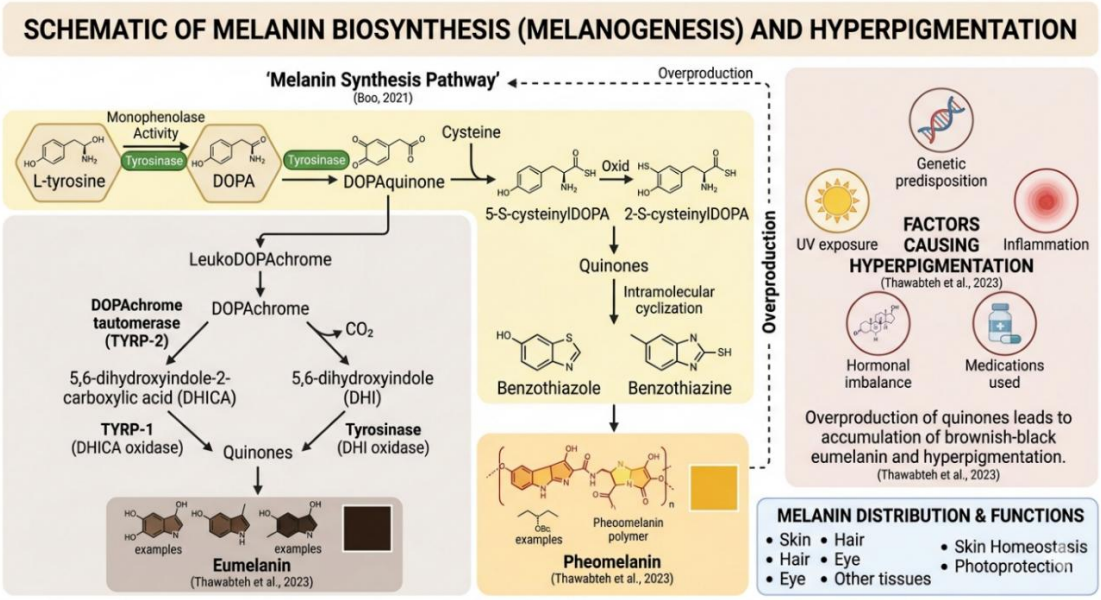

Figure 2. Pathway of Melanin Synthesis. (Generated using Google Gemini AI).

Keratinocyte-derived endothelin-1 (ET-1) represents another important paracrine regulator of melanogenesis. Following UV irradiation, keratinocytes release ET-1, which binds to endothelin B receptors (ETBR) expressed on melanocytes. This interaction activates phospholipase C (PLC), protein kinase C (PKC), MAPK, and intracellular calcium signaling pathways, ultimately increasing MITF activity and the expression of melanogenic enzymes including tyrosinase, TYRP1, and TYRP2. In addition to stimulating melanin synthesis, ET-1 promotes melanocyte proliferation, dendrite elongation, and melanosome maturation, thereby facilitating more efficient pigment transfer to surrounding keratinocytes. The synergistic interaction between ET-1 and α-MSH further potentiates UV-induced pigmentation, highlighting ET-1 signaling as an attractive therapeutic target for pigmentary disorders such as melasma and post-inflammatory hyperpigmentation [12,13]. The Wnt/β-catenin and ET-1 pathway are summarized in Figure 3.

Emerging evidence also indicates that hyperpigmentation is regulated through epigenetic modifications and intercellular communication mediated by extracellular vesicles. In melasma, altered DNA methylation patterns, histone acetylation, and microRNA expression have been reported to modulate genes involved in melanogenesis, inflammation, oxidative stress, and extracellular matrix remodeling, thereby contributing to the chronic and recurrent nature of the disease [14,15]. Furthermore, melanocytes actively communicate with neighboring keratinocytes through exosome-mediated melanin transfer. Exosomes containing melanosomal proteins, microRNAs, and melanogenic regulatory molecules enhance pigment transfer independently of classical dendrite-mediated mechanisms while simultaneously influencing melanocyte differentiation and inflammatory responses. UV radiation has been

shown to increase exosome secretion, thereby amplifying pigmentation through enhanced intercellular signaling. These newly recognized molecular mechanisms provide additional therapeutic opportunities beyond direct tyrosinase inhibition, including interventions targeting extracellular vesicle biogenesis, epigenetic modulation, and melanocyte stem cell signaling [9].

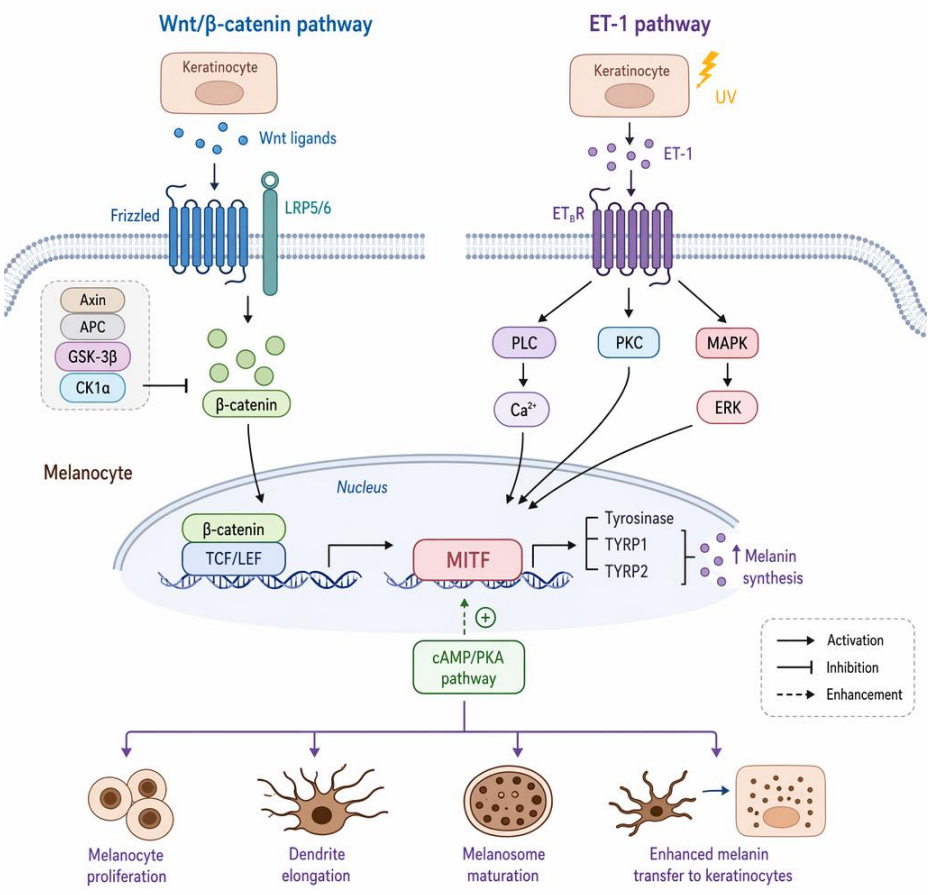

Figure 3. Wnt/β-catenin and ET-1 pathway.

2.1. UV Exposure

UV radiation is the most significant environmental factor that causes hyperpigmentation. Exposure to solar UV, specifically UVA and UVB rays, could initiate a complex cellular cascade of melanocytes to protect the skin from damage [10]. This protective response known as melanogenesis. The mechanisms include direct effects on the keratinocytes to release pro-inflammatory cytokines, direct effects on the DNA, depletion of cellular antioxidants as well as generation of reactive oxygen species (ROS) and production of other inflammatory mediators [16,17].

Upon UV exposure, keratinocytes and melanocytes rapidly generate ROS. These ROS result from direct photo-chemical excitation of endogenous chromophores and indirect

secondary processes, such as mitochondrial dysfunction and NADPH oxidase activation. The accumulation of ROS causes oxidative damage to DNA, lipids, and proteins and depletes endogenous antioxidant defenses [18]. Such oxidative stress is a pivotal upstream driver of melanogenic activation in the epidermis.

Figure 4 illustrates the UV-induced melanogenic pathway, from p53-mediated α-MSH release and MC1R activation to melanin synthesis and the transfer of mature melanosomes from melanocytes to keratinocytes. In the basal-epidermal melanocyte unit, keratinocytes act not merely as passive recipients of melanin but as active drivers of melanogenesis. UV irradiation of keratinocytes induces expression of p53, which increases pro-opiomelanocortin (POMC) gene expression to yield α-MSH and ACTH. These ligands bind to the MC1R on melanocytes, elevating intracellular cAMP and activating the MITF transcriptional network that increases tyrosinase and TYRP1/2 expression [19]. In parallel, UV-exposed keratinocytes secrete ET-1, stem-cell factor (SCF)/Kit ligand, hepatocyte growth factor (HGF), and various cytokines (IL-1, IL-6, TNF-α), which further stimulate melanocyte proliferation, dendrite formation, and melanin synthesis [12,20].

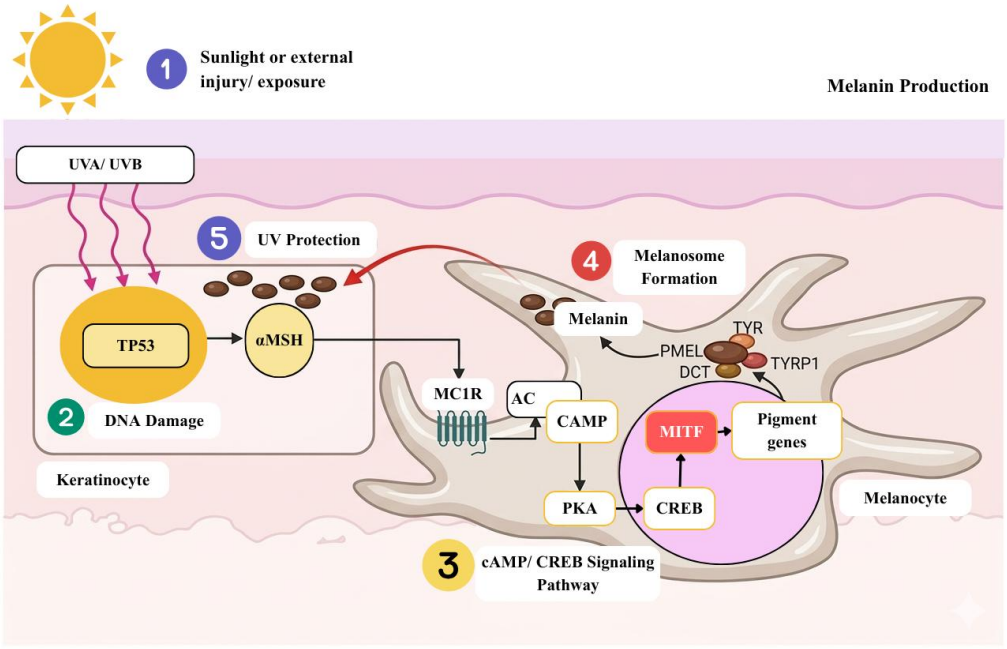

Figure 4. Melanin production in skin. (1) Melanogenesis activated upon UV exposure; (2) UV radiation damages the DNA in the keratinocyte, activating the p53 pathway, which results in the production of αMSH. αMSH is secreted from the keratinocytes and binds to the MC1R on the melanocyte. (3) cAMP levels are then increased within the melanocytes, activating protein kinase A (PKA). PKA activation induces the recruitment of CRE-binding (CREB) protein and thereby the transcriptional activity of MITF. (4) MITF activates the transcription of pigment genes, including TYR, TYRP1, DCT, and PMEL, which are transported to the membrane-bound melanosome. (5) Matured melanosomes are then transferred from melanocytes to keratinocytes to protect them against UV light (Created with Canva, modified using Google Gemini AI).

2.2. Genetic Predisposition

Melanogenesis is a process that is controlled by a complex interaction between genetic programming and environmental factors, mainly UV light and inflammation [21]. The frequent familial occurrence together with positive reports of family history often suggests an inherited predisposition [22]. This genetic basis includes differences in genes that control hormone receptors, melanocyte function and skin's reaction to external stimuli. For instance, changes in an individual's susceptibility to hyperpigmentation have been linked to polymorphism in genes encoding the MC1R which is essential for melanogenesis [15]. The activation of MC1R by its ligand such as α-MSH, stimulates cAMP signaling, promoting eumelanin synthesis [23]. On other hand, MC1R dysfunctional variations interfere with this pathway and promote the synthesis of more pheomelanin. These variations are more common in European populations and are closely linked to red hair, lighter skin, more freckles and increase risk of melanoma. Additionally, genetic variations can affect the transcription factor like MITF which may result in a stronger and long-lasting melanogenic response to stimuli like UV exposure or inflammation [21]. In summary, the threshold at which a person's skin will react to a stimulus with pathological hyperpigmentation is set by their innate genetic composition.

2.3. Inflammation

Inflammation is another factor that contributes to hyperpigmentation specifically PIH. PIH is not simply the result of a single inflammatory event but a complex cascade of cell-cell interactions that leads to uncontrolled melanin production [24]. The process begins with an inflammatory insult like acne or eczema which later triggers the release of inflammatory mediators from keratinocytes and infiltrating immune cells. These include prostaglandins, leukotriene (LT), cytokines and reactive oxygen species (ROS) [25].

Figure 5 summarizes the major inflammatory mediators and signalling pathways involved in melanocyte activation, increased melanin synthesis, and the development of post-inflammatory hyperpigmentation. Key mechanisms of the PIH are melanocyte stimulation, basal layer damage and dermal melanosis. In melanocyte stimulation, inflammatory mediators like interleukin (IL), prostaglandins (PG), LT and tumor necrosis factor (TNF) directly stimulate the melanocytes resulting in melanin production. Those inflammatory mediators are mainly triggered by inflammatory cells and ROS [24]. PG and LT bind to specific receptors located on melanocyte cell membrane and trigger the activation of various signaling pathway that can lead to proliferation and differentiation of melanoblasts into melanocytes. Meanwhile, IL groups and TNF can stimulate dermal fibroblast to release melanocyte-stimulating factors including HGF, SCF and keratinocyte growth factor (KGF) [24]. Later,

those inflammatory mediators will upregulate the expression of tyrosinase, the rate-limiting enzyme in melanin synthesis, leading to an accelerated conversion of L-tyrosine to dopaquinone [22]. In severe inflammation, the basement of membrane may be disrupted allowing melanin to leak into dermis. This dermal melanin will be engulfed by macrophages forming melanophages that persist longer than epidermal pigment and making it difficult to treat [21].

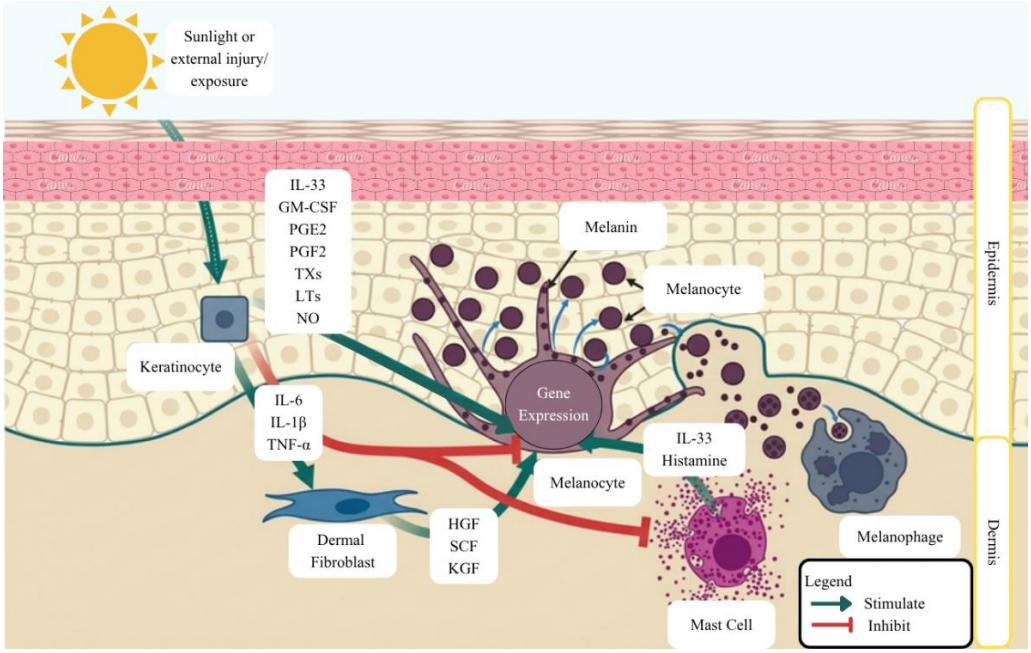

Figure 5. Mechanism of PIH through various inflammatory mediators' pathway (Created with Canva, modified using Google Gemini AI).

2.4. Hormonal Imbalance

Women are commonly having pigmentation issue especially during reproductive hormone fluctuation. Estrogen and progesterone are strongly implicated as important roles in its pathogenesis due to their association with pregnancy, oral contraceptive use and hormone replacement therapy (RCT) [22].

Melanocytes are biologically active cells that express estrogen and progesterone receptors which is the melanocyte-stimulating hormone (MSH) receptors. Binding of hormonal ligands to this receptor initiate a series of intracellular processes. Tyrosinase has been demonstrated to be activated by estrogen, which also directly increases the activity of melanocyte proliferation. It can also increase the transcription of melanogenesis-related genes such as tyrosinase and TRP-1 [21]. Furthermore, estrogen increases melanocytes dendricity which can improve their capacity to transfer melanin-rich melanosomes to nearby keratinocytes, thereby intensifying pigmentation. Progesterone role is slightly more complex

than estrogen. Some studies suggest that progesterone can also stimulate melanogenesis while some studies suggest that progesterone may contribute by modulating the local inflammatory or vascular environment in the skin [15]. The net result of these hormonal signals is the creation of a hyper-functional melanocyte population that is primed to overproduce melanin, especially when triggered by secondary factors like UV exposure. This hormonal priming explains why melasma is often chronic and difficult to manage, as the melanocytes remain in a sensitized state long after the initial hormonal trigger like pregnancy has passed. In summary, elevation of these hormones can upregulate the expression of MSH receptors [3]. This makes the melanocyte to be more sensitive even with just a little UV exposure.

Besides, hormone could also contribute to melanocortin system activation. The hormonal shift can stimulate the production of ACTH and α-MSH. These molecules bind to the MC1R on the surface on melanocytes thereby triggering a secondary messenger system like cAMP to increase melanin production [22]. Last but not least, hormonal imbalance can also affect the vascularity of the skin. Increased vascular endothelial growth factor (VEGF) in melasma-affected skin suggests that hormones may interact with the underlying blood vessels to sustain pigmentary changes [21].

2.5. Medication Used

There are many drugs that can cause hyperpigmentation by several mechanisms. The appearance and location of the hyperpigmentation may give a hint to the causative drug. The pathogenesis of the hyperpigmentation can be divided into three broad mechanisms which are the promotion of melanin production and the accumulation of the drugs or its metabolites. Simulation of melanin synthesis could cause by certain drugs like antimalarial that can bind to melanin with high affinity. While this binding can directly contribute to pigmentation and causes more melanin production. Some chemotherapeutic agents also can upregulate the melanogenic pathway. Other than that, certain medications like minocycline can breakdown into reactive quinone-like metabolites can chelate iron and deposit blue-blank pigments in skin, scar and sun-exposed areas. These are insoluble and can accumulate in dermal macrophages and elastic fibers [26].

2.6. Skin Microbiome Disruption

Skin microbiome plays an important role in maintaining skin homeostasis and regulating immune responses. Recent studies suggest that hyperpigmentation is linked to dysbiosis. These microbial communities do not just passively reside within the epidermis but

also play an active role in the maintenance of epidermal homeostasis and help protect the epidermis from UV-induced oxidative stress.

One important pathophysiology pathway that microbe's metabolism induced hyperpigmentation includes porphyrins produced by *Cutibacterium acnes.* The study by Meunier *et al*. [27] reported that porphyrins such as coproporphyrin III and photoporphyrin IX were capable of diffusing into the stratum corneum and accumulating in live epidermal cells. As a result, ROS were formed and there was an increased expression of IL-8. In turn, this inflammatory and oxidative stress resulted in stimulation of melanin synthesis due to activation of the TSPO/PBR protein located on mitochondrial membranes and participating in porphyrin transport and steroidogenesis. Clinically, it has been shown that the content of porphyrins correlates positively and significantly with the intensity of brown spots and invisible hyperpigmentation, thus making a clear connection between the microbe-produced metabolites and the pathophysiology of hyperpigmentary disorders caused by aging [28].

Dysbiosis of *C. acnes* compared to other bacteria causes inflammation during which keratinocytes produce pro-inflammatory cytokines such as IL-1α, TNF-α and IL-6. These mediators attach to the toll-like receptors in melanocytes and activate the intracellular signaling pathway like p38 MAPK and NF-κB, leading to increased expression of tyrosinase and MITF genes involved in melanogenesis [28]. The reason for which inflammation acne is associated with prolonged hyperpigmentation is that the inflammatory pathway caused by microbes has a lasting effect on the activity of melanocytes. Moreover, the authors found that bacteria *Eikenella corroden*s occurs in large amounts in hyperpigmented skin and can influence the regulation of melanin synthesis through its preservation, while *Kocuria species* that have antioxidant activity are more common in less pigmented skin.

Staphylococcus epidermidis, a dominant skin commensal bacterium, is known to secrete lipoteichoic acid (LTA), which stimulates TLR2 in the keratinocytes. The stimulation leads to release the stem cell factor (SCF), which then attracts the mast cells into dermis and triggers their degranulation. It has been found that the dermal mast cell count is significantly increased in melasma-affected skin and that the histamine secreted by these cells directly promotes the activity of the melanocytes and leads to an increase in the synthesis of melanin [28].

3. Conventional and Emerging Cosmeceutical Approaches

3.1. Hydroquinone

Topical agents are widely used for the treatment or management of site-specific skin hyperpigmentation. Hydroquinone, a gold standard for anti-hyperpigmentation, has been used in topical applications since the 1960s. It can inhibit the tyrosinase from interfering with melanin synthesis [22]. Structurally resembling tyrosinase, HQ acts as a competitive substrate analogue that binds reversibly to the active tyrosinase site and interferes with the copper-containing catalytic domain. Thus, binding kinetics is characterized by hydroquinone's higher affinity for the oxidized form of tyrosinase compared to the native reduced form, effectively trapping the enzyme in an inactive state and reducing melanin polymer formation [29]. Besides, it can also interfere with melanosome formation and promotes selective damage to melanocytes, thereby reducing melanin synthesis and accumulation in epidermis [1,30].

Additionally, some studies also suggested that hydroquinone may accelerate the degradation of melanosomes and inhibit DNA and RNA synthesis within melanocytes, further contributing to its depigmentation effects [30,31]. Study done by Nishityama *et al*. [29] to show the molecular pathway of the HQ in reducing pigmentation in the retinal pigment epithelial (RPE) cells in the short term and long-term observation. The gene expression in melanin-production pathway of dopachrome tautomerase (DCT) and TYRP1 were downregulated in short term exposure. Interestingly, the study noted that while cellular melanin concentration dropped significantly within 24 hours, the transcription levels of the human tyrosinase did not change significantly. This indicates that HQ immediate molecular impact in these cells is achieved by selectively bottlenecking the downstream machinery rather than shutting down the transcription of the primary upstream enzyme. Meanwhile in long-term exposure of higher dose of HQ for a week, the molecular dynamics shift. DCT and TYRP1 still remained suppressed but the total melanin content elevated due to compensatory mechanisms. The research proposed that higher dose of HQ could trigger the upregulation of MC1R mRNA expression.

Beyond enzyme inhibition, HQ exhibits therapeutic efficacy through pro-oxidation mediation. Under physiological conditions, HQ undergoes auto-oxidation to generate benzoquinone and superoxide anions, which subsequently produce hydrogen peroxide and hydroxyl radicals through Fenton-type reaction [30]. The ROS generation serves as a dual role in contributing to hyperpigmentation. Firstly, ROS directly inactivate tyrosinase by oxidizing its essential copper ions from Copper (II) ions to Copper (III) ions. This creates irreversible oxidation that disrupts the enzyme catalytic cycle and prevents melanin synthesis [31]. Second, the oxidative stress inflicted by HQ-derived ROS selectively damages melanocytes by inducing lipid peroxidation of cellular membranes, protein carbonylation, and mitochondrial dysfunction [1,30]. This oxidative damage to melanosomes further accelerates melanosome

degradation, impairing the transfer of melanin to keratinocytes and reducing epidermal pigmentation.

Though it is effective, it can lead to different side effects like irritation and ochronosis. The use of this ingredient in cosmetics has been banned since 2001 because of the high risk of carcinogenesis in case of prolonged exposure to hydroquinone [10]. However, hydroquinone is now being used back in the market but the dosage for hydroquinone is prescribed at 4%and below to prevent possible side effects. Other than side effects, its stability also remains a big challenge. According to Ghanbarzadeh *et al*. [32], hydroquinone is susceptible to oxidation and browning of hydroquinone is a sign of oxidative degradation. The chemical instability of hydroquinone later can lead to the formation of p-benzoquinone which is carcinogenic [33].

Despite challenges, it remains advantageous due to its strong tyrosinase-inhibiting activity, well-documented clinical efficacy, and relatively rapid depigmenting effect compared with many other topical agents. Numerous dermatological studies have shown hydroquinone's clinical efficacy. For instance, a prospective, randomized, double-blind clinical study by Wu *et al*. [34] used a split-body design to compare topical hydroquinone with hexylresorcinol and found that hydroquinone treatment significantly improved the appearance of skin pigmentation. Similarly, Lin and Zhu [35] assessed the use of hydroquinone cream and tranexamic acid in conjunction with photorejuvenation therapy for patients with complex facial pigmentation and discovered that, when compared to traditional treatment, the combined regimen greatly reduced the severity of pigmentation and improved the overall appearance of the skin. These studies demonstrate the efficacy of hydroquinone as a depigmenting agent and its ongoing significance in the treatment of hyperpigmentation disorders in clinical dermatology.

3.2. Arbutin

Another agent which is a derivative of hydroquinone, arbutin, is also used to treat hyperpigmentation. It offers a gentle alternative compared to hydroquinone by slowly releasing hydroquinone and inhibiting tyrosinase with lower irritation risk, making it suitable for sensitive skin [36]. The primary mechanism of action of arbutin involves the inhibition of tyrosinase which is the key enzyme responsible for melanin biosynthesis. According to Boo [10], arbutin suppresses melanogenesis by competitively inhibiting tyrosinase activity, thereby preventing the oxidation of L-tyrosine to L-DOPA and the subsequent formation of melanin. In addition, arbutin exhibits antioxidant properties that reduce oxidative stress within melanocytes, which is known to stimulate melanin production. The compound may also downregulate the expression of melanogenesis-related proteins such as TYRP1 and TYRP2,

further suppressing melanin synthesis. Through these combined mechanisms, arbutin effectively decreases melanin formation and contributes to the gradual lightening of hyperpigmented skin [10,37].

The effectiveness of arbutin as anti-hyperpigmentation agent has been shown in a few studies. Arbutin demonstrated strong inhibitory activity against melanogenesis, confirming its efficacy as a depigmenting agent, according to Sun *et al.* [38], who assessed several anti-hyperpigmentation compounds using high-throughput screening models. In the study, arbutin showed inhibition of tyrosinase activity and reduced melanin synthesis in B16-F10 cells in dose-dependent manner. Furthermore, the strong melanogenesis-inhibitory potential of the arbutin structure was highlighted by Peyrot *et al.* [39], who synthesized arbutin analogs through enzymatic modification and found increased antipigmentation activity in some derivatives. In their study, S-2 compound containing a D-galactosyl unit was found to be a better derivative in inhibiting tyrosinase activity and providing better stability. Additionally, Patel and Jadeja [40] created phosphatidylcholine complexes of arbutin to enhance its stability and skin penetration, showing improved skin-whitening efficacy in formulation studies. These results validate the use of arbutin in dermatological and cosmetic applications as an efficient and extensively researched depigmenting substance.

Despite its advantages, several limitations associated with arbutin have been reported. The issue arises when arbutin apply alone, where the depigmenting effects are slightly lower than hydroquinone [41]. Furthermore, arbutin may undergo hydrolysis under certain conditions like exposure to high temperature and UV and release hydroquinone, which later raises concerns regarding stability and safety in some formulation [37]. However, compared to hydroquinone, arbutin has several advantages as an anti-hyperpigmentation agent, such as reduced cytotoxicity, enhanced safety profile, and a lower risk of side effects like skin irritation or ochronosis. Because of these qualities, arbutin is now frequently used in cosmetic formulations for skin lightening and pigmentation control, especially in long-term use products [10,41].

3.3. Kojic Acid

Kojic acid is another tyrosinase inhibitor derived from fungal metabolites such as *Aspergillus sp.* and *Penicillium sp.* that chelates sopper at the enzyme site, thereby reducing melanin synthesis [41]. Studies suggested that kojic acid to be used at 1% to prevent any irritation during application. Primary mechanism of kojic acid mainly involves direct inhibition of tyrosinase which is responsible to convert L-tyrosinase to L-3,4-dihydroxyphenylalanine [43, 44]. Tyrosinase is a type-3 copper protein which has copper A and

copper B at its active site, each are coordinated by three coordinate-covalent bonds to surrounding histidine residues. These copper ions are essential for capturing molecular oxygen to initiate the melanogenesis cascade [44]. Kojic acid acts predominantly as a competitive inhibitor of tyrosinase by mimicking the phenolic structure of its natural substrate, L-tyrosinase. The molecular mechanism of this inhibition is driven by kojic acid potent metal-chelating capability which is mediated by the α-hydroxyketone moiety. Upon docking of kojic acid within the catalytic pocket, the oxygen molecules become bidentate ligands that donate electrons for stable bonding with the binuclear copper center. Kojic acid becomes linker between these two coppers and change in structure hinders the interaction of copper with oxygen which is needed for the activation of peroxide-bridged oxy-tyrosinase state. By chelating the copper ions at the tyrosinase active site, kojic acid stops tyrosine and L-DOPA from being catalytically oxidized into precursors of melanin [42, 45]. Kojic acid not only inhibits tyrosinase but also demonstrates antioxidant activity that lowers reactive oxygen species involved in melanogenesis, which further suppresses the production of melanin. Kojic acid is a reducing agent where it can reduce the o-dopaquinone back into L-DOPA therefore preventing the reactive quinone intermediates from polymerizing into dark eumelanin or pheomelanin pigments. Besides, Maddaleno *et al*. [46] also reported that kojic acid exerts moderate suppressive effects on MITF by mitigating the ROS induced by UV rays. Kojic acid successfully lowers melanin production and aids in lightening hyperpigmented skin regions through these mechanisms [46].

Numerous experimental and formulation studies have shown that kojic acid is effective in reducing hyperpigmentation. For example, using an environmentally friendly preparation method, Saeedi *et al*. [47] created kojic acid-loaded niosomes and reported significant anti-melanogenesis and antioxidant effects when compared to the free compound. In both in-vitro and in-vivo tests, the niosomal formulation demonstrated better skin penetration and increased depigmenting efficacy while maintaining favorable safety profiles. Similar to this, Omidi *et al*. [48] formulated kojic acid within green alginate nanoparticles and showed potent melanogenesis-inhibiting activity in both in-vitro and in-vivo studies, indicating that kojic acid's skin-whitening potential may be enhanced by nano-delivery systems. Other than that, Tetali *et al*. [49] conducted a 12-week clinical trial to examine the efficacy of kojic acid in patients with dyschromia. The study revealed a better improvement in dyschromia appearance, skin tone and radiance when treated with kojic acid and vitamin C compared to hydroquinone alone. In this study, volunteers also reported less stinging and tightness to skin indicated a good tolerance of kojic acid in topical formulation. These studies demonstrate the ongoing interest in enhancing kojic acid delivery methods to optimize its therapeutic benefits in the treatment of hyperpigmentation.

Though it is effective, kojic acid itself has stability issues and potential for irritation have led to its combination with stabilizing agents in the formulations [44]. Reported in Waarzynczak [45], kojic acid is susceptible to oxidation when exposed to light, heat and air which may reduce the efficacy over time. Moreover, irritation is also reported when topical application of kojic acid is at a higher concentration [42]. Some individuals experienced contact dermatitis, erythema and skin irritation when kojic acid is applied at higher concentration above 2% (w/v) [44]. Nevertheless, kojic acid offers several advantages as an anti-hyperpigmentation agent, including strong tyrosinase-inhibiting activity, natural origin, and its ability to act synergistically with other depigmenting agents in combination therapies. Due to these benefits, kojic acid remains a widely utilized ingredient in cosmetic and dermatological formulations aimed at controlling excessive melanin production and improving skin tone uniformity.

3.4. Azelaic Acid

Azelaic acid is a dicarboxylic acid and used in cosmeceutics for anti-pigmentation. It mainly acts on tyrosinase to inhibit the production of melanin and oxidoreductase enzymes involved in melanogenesis. By suppressing these enzymes, it can limit the melanin production in melanocytes. At molecular level, azelaic acid has been reported to interfere with signaling pathways that regulate the expression of MITF, the master transcription factor controlling melanogenesis. MITF governs the transcription of melanogenic genes including tyrosinase, TYRP1 and TYRP2 [50]. Suppression of MITF expression consequently leads to reduced transcription and translation of these melanogenic enzymes, thereby decreasing melanin biosynthesis. Moreover, MITF downregulation attenuates melanocyte differentiation and melanogenic activity. Study from Kumari *et al*. [50] suggests that azelaic acid may modulate intracellular signaling cascades involved in MITF regulation, including pathways associated with cAMP and cAMP-response element binding protein (CERB). Inhibition of CERB phosphorylation may contribute to reduced MITF transcription and further suppress the downstream melanogenic genes as it functions as a major transcriptional activator of MITF.

Additionally, azelaic acid exhibits selective cytotoxic and antiproliferative effects on abnormal or hyperactive melanocytes without significantly affecting normal melanocytes, making it particularly useful in conditions such as melasma and post-inflammatory hyperpigmentation [51]. Some article also reported the antioxidant and anti-inflammatory activities that help reduce oxidative stress and inflammatory mediators that can stimulate melanogenesis [52, 53]. Furthermore, recent studies have suggested that azelaic acid may interfere with melanin transfer from melanocytes to keratinocytes, thereby further

contributing to the reduction of visible skin pigmentation [9]. Due to its two carboxyl groups, azelaic acid is easily to be ionized and exhibits poorer skin penetration [54]. Conventional topical formulations often exhibit a slow onset and require a prolonged or consistent application to see the improvement in hyperpigmentation [51]. In addition, some individuals may experience mild skin irritation, erythema and dryness [53]. Though with these challenges, the toxicity is still lower as compared to hydroquinone and therefore it is still suitable for long term usage.

Azelaic acid has been shown in numerous studies to be useful in treating hyperpigmentation. Topical azelaic acid formulations can considerably lessen the severity of melasma and other pigmentary disorders when applied consistently, according to clinical and formulation-based research [55]. For instance, Petrovici *et al*. [51] compiled a number of clinical findings showing that the combined anti-melanogenic and anti-inflammatory qualities of azelaic acid creams and gels effectively reduce hyperpigmented lesions and improve skin tone uniformity. Furthermore, Arshad *et al*. [56] created a gel of mesoporous silica nanoparticles loaded with azelaic acid to improve drug stability and skin penetration. In comparison to traditional formulations, their study showed increased depigmenting activity and delivery efficiency, indicating that nanotechnology-based delivery systems may further boost azelaic acid's therapeutic potential in pharmaceutical and cosmetic applications.

3.5. Tranexamic Acid

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that can be used as an anti-fibrinolytic [56]. It has shown depigmenting effects by interfering with plasmin-mediated inflammatory pathways in keratinocytes, which reduces melanocyte tyrosinase activity when apply topically [57]. Mechanism proposed was inhibiting the tyrosinase receptor and depleting the keratinocyte pool or arachidonic acid involved in the UV-induced melanogenesis [58]. Inflammation and UV light can cause keratinocytes plasminogen activator to become more active, converting plasminogen to plasmin. In turn, plasmin encourages melanocyte activation and the release of inflammatory mediators like prostaglandins and arachidonic acid. TXA successfully stops this cascade by competitively blocking plasminogen's binding to its receptor, which lowers melanocyte stimulation and subsequent melanin synthesis [59]. At molecular level, UV radiation increases the expression of urokinase-type plasminogen activator (uPA) in keratinocytes, resulting in enhanced conversion of plasminogen to plasmin. This will promote the release of arachidonic acid from membrane phospholipids through phospholipase A2 activation. Arachidonic acid is subsequently metabolized via cyclooxygenase and lipoxygenase pathways to generate PG and LT [58]. These

inflammatory mediators stimulate neighboring melanocytes by increasing cAMP level and PKA leading to enhanced expression of MITF and its downstream melanogenic enzymes. TXA prevents the formation of plasmin by suppressing the generation of these pro-melanogenic inflammatory mediators and indirectly attenuates MITF-mediated melanogenesis. Besides, inhibition of plasmin activity reduces the release of basic fibroblast growth factors (bFGF), α-MSH and other melanocyte-activating factors from keratinocytes, further limiting melanocytes proliferation and melanin synthesis.

A recent study by Cho *et al*. [60] found that TXA induces autophagy in melanoma cells by activating signaling pathways such as MAPK/ERK and increasing the expression of autophagy-related proteins. This activation leads to the degradation of tyrosinase and melanosomes, thereby reducing pigmentation. ERK phosphorylation influences melanogenesis through several downstream mechanisms. Sustained ERK activation promotes phosphorylation of MITF at specific serine residues which target MITF for ubiquitination and subsequent proteasomal degradation. The reduction in MITF protein levels decreases transcription of melanogenic genes like tyrosinase and diminishes melanin synthesis. Other than that, ERK activation stimulates autophagic processes characterized by increased expression of autophagy-related proteins such as Beclin-1, LC3-II and ATG proteins [60]. Enhanced autophagic flux facilitates the lysosomal degradation of melanosomes and melanogenic enzymes, particularly tyrosinase. As a result, TXA provides dual anti-melanogenic effect through MAPK/ERK signaling and autophagic clearance of existing melanosomes.

Over the years, much research was performed and demonstrated a good anti-pigmentation effect of oral TXA. In a prospective, open-label study in China by Li *et al*. [61], 35 individuals were involved by receiving oral TXA three times per day. As a result, 85% of the subjects showed a good improvement in VISIA photo after 4 weeks and 100% of the subject achieve overall improvement in VISIA photo after 16 weeks. Besides, a pivotal study by Qi *et al*. [59] addressed the issue of poor TXA penetration and developed into a functionalized self-assemble micelles. They produced TXA-loaded nanocarriers with an average size of about 176 nm using materials derived from plants. When compared to a free TXA solution, in vitro results showed that these micelles greatly improved skin penetration and retention. Additionally, the nanocarrier system demonstrated a superior capacity to suppress tyrosinase activity and melanin synthesis in melanoma cells, confirming that better delivery directly results in increased therapeutic efficacy.

The use of TXA as anti-pigmentation agent is considered off-label by the Food and Drug Administration (FDA) due to its potential side effect to cause thrombosis. Hydrophilicity of TXA is also causing it to have poor skin penetration, therefore modifying such compounds through nanotechnology is required. Conventional topical formulations often fail to deliver a sufficient concentration of the TXA to the basal layer of the epidermis and the dermis where melanocytes and the vascular targets reside [62]. Despite the challenges, TXA is still widely used and usually combined with other anti-pigmentation agent like kojic acid, arbutin to achieve a synergistic effect.

3.6. Microbiota Metabolites

Skin microbiomes have recently emerged as a promising therapeutic target in cosmeceutical research due its role in maintaining the skin homeostasis, immune regulation and pigmentation balance [63]. More research suggests that microbiota-derived metabolites, probiotic, and postbiotics can modulate the melanogenesis through different mechanisms in inhibiting melanogenesis. These microbiome-associated approaches have therefore gained attention as potential alternatives or adjuncts to conventional depigmenting agents with improved biocompatibility and reduced adverse effects. Microbial metabolites produced by commensal skin bacteria have demonstrated significant anti-melanogenic activity. Kao *et al*. (2021) [64] reported that propionic acid generated through fermentation activity of *Cutibacterium acnes* effectively reduced UVB-induced melanin synthesis by supressing the tyrosinase activity via binding to free fatty acid receptor 2 (FFAR2). The study found that though fermentation process was done by *C. acne*, the inhibition activity of the metabolite did not disrupt the proliferation of melanocytes and balance of skin microbiome. Similarly, Sekino *et al*. (2024) [65] isolated a cyclic dipeptide derived, cyclo (L-Pro-L-Tyr), from *Corynebacterium tuberculostearicum* and tested with mushroom tyrosinase. The docking simulation suggests that cyclo (L-Pro-L-Tyr) enters the substrate pocket and binds to His263 and Val283 to inhibit the tyrosinase activity. However, the study only evaluated through molecular docking on mushroom tyrosinase, more in-vitro test could be done to study on more possible mechanisms of cyclo (L-Pro-L-Tyr) as potential anti-melanogenic agent. Besides that, Wu *et al*. (2023) [66] reported that whole lysate and bacterial lysate of *Bifidobacterium longum* Strain ZJ1 ferments efficiently decrease the α-MSH-induced melanin upregulation and reduced intracellular tyrosinase activity in B16-F10 cells. The study also suggests that the ferments could modulate the α-MSH through the inhibition of four melanogenesis-related genes such as MITF, TYR, TRP-1 and TRP-2. Findings above indicate that the microbiome-based therapeutics represent a rapidly expanding strategy in anti-hyperpigmentation treatment

through their ability to regulate melanogenesis, oxidative stress, and skin inflammation simultaneously.

3.7. Phytochemicals

Phytochemicals are natural compounds that are extracted from botanical sources. These compounds include flavonoids, phenolic acids, carotenoids, and other secondary metabolites can inhibit tyrosinase activity, suppress melanogenesis-related signaling pathways, and provide antioxidant effects that reduce oxidative stress involved in melanin production. Because oxidative stress and inflammation can stimulate melanocyte activity, the antioxidant and anti-inflammatory properties of phytochemicals play an important role in reducing excessive melanin synthesis and improving skin pigmentation disorders. The structure-activity relationship (SAR) of these phytochemicals is primarily dictated by the presence and position of hydroxyl group on their aromatic rings, which are critical for both tyrosinase binding and radical scavenging activity. Specifically, the catechol moiety confers high affinity for the copper ions in the tyrosinase active site through bidentate chelation, while additional hydroxyl substitutions at the 5- and 7-positions on flavonoid rings enhance electron-donating capacity, thereby potentiating ROS neutralization and metal ion chelation. Furthermore, the presence of a C2 and C3 double bond conjugated with a 4-oxo group in the C-ring of flavonoids stabilizes the molecular conformation for optimal enzyme docking and increases the compound's redox potential, which is essential for both tyrosinase inhibition kinetics and antioxidant efficacy.

As an example, hesperidin, a flavonoid obtained from various citrus fruits, exhibits anti-tyrosinase and photoprotective activity. A study was done by Zhu & Gao (2008) [67], showed that hesperidin can inhibit the melanin synthesis on melanocyte through dose-dependent tyrosinase enzyme inhibition. The SAR of hesperidin reveals that its 4'-methoxy group and rutinose sugar moiety at the 7-position modulate its hydrophilicity and membrane permeability, while the 3',5'-dihydroxyl pattern on the B-ring provides the structural basis for copper chelation at the tyrosinase active site. Besides, a study performed by Gao *et al*. (2021) [68] investigated the anti-melanogenic activity of enriched extracts from *Pueraria lobata* stems and reported a significant inhibition of tyrosinase activity and melanogenic synthesis through in-vitro testing of mRNA expression of tyrosinase. In the study, in-silico analysis was done and puerarin and daidzin were identified for good affinity in binding for human tyrosinase. The SAR of these isoflavones demonstrates that the 7-hydroxyl group and the C-glucosyl moiety at the 8-position in puerarin facilitate hydrogen bonding with tyrosinase residues, whereas daidzin's 7-hydroxy-4'-hydroxy pattern allows for bidentate chelation of the

binuclear copper center, contributing to its competitive inhibition kinetics. Yu *et al*. (2025) [69] also did a study on *Lilium lancifolium* Thunb flower extraction for anti-pigmentation study. The study revealed a good anti-pigmentation effect on zebrafish embryo-based whitening model during the green bud phase of the plant. The tyrosinase activity was reduced by 73.74% and melanin content was reduced to 54.85% of the control as during this green bud phase, the plant produced higher phytochemical extraction for a better effect. The enhanced efficacy during the green bud phase is attributable to the accumulation of flavonoid glycosides bearing ortho-dihydroxyl moieties on their B-rings, which maximizes both tyrosinase binding affinity through copper coordination and ROS scavenging capacity through electron transfer mechanisms.

Despite their promising potential, the use of phytochemicals in anti-pigmentation formulations also presents certain challenges. Variability in phytochemical composition due to differences in plant species, cultivation conditions, and extraction methods can affect the consistency and efficacy of these compounds. Furthermore, some phytochemicals may exhibit limited skin penetration or stability in topical formulations, which can reduce their therapeutic effectiveness. Nevertheless, phytochemicals offer several advantages, including natural origin, multifunctional biological activities such as antioxidant and anti-inflammatory effects, and generally lower risk of adverse reactions compared with synthetic depigmenting agents. As a result, phytochemical-based compounds are increasingly being explored as alternative or complementary agents for the treatment of hyperpigmentation in modern cosmeceutical research. An overview of the major depigmenting agents and their classification according to their mechanisms of action is presented in Table 1.

Table 1. Classification of depigmentation agents based on their mechanism of action.

Anti-melanogenic Agents	**Proposed Mechanisms of Action**	**Citation**
Hydroquinone	Acts as a competitive substrate analogue that reversibly binds to the tyrosinase active site, specifically trapping the enzyme in an inactive state due to a higher affinity for its oxidized form.	[22]
	Interfere with melanosome formation and promotes selective damage to melanocytes.	[1, 30]
	Accelerate the degradation of melanosomes and inhibit DNA and RNA synthesis within melanocytes. Generates ROS like superoxide anions, hydrogen peroxide, and hydroxyl radicals via auto-oxidation and Fenton-type reactions under physiological conditions.	[30, 31]
Arbutin	Inhibition of tyrosinase by preventing the oxidation of L-tyrosine to L-DOPA and the subsequent formation of melanin.	[10]

	Provide antioxidant effects and downregulate the expression of melanogenesis-related proteins such as tyrosinase-related protein-1 (TRP-1) and TRP-2.	[10, 37]
Kojic acid	Inhibition of tyrosinase by chelating copper ions.	[42, 45]
	Provide antioxidant effects by lower the reactive oxygen species.	[45]
Azelaic acid	Inhibition of tyrosinase and exhibits selective cytotoxic and antiproliferative effects on abnormal or hyperactive melanocytes.	[51]
	Provide antioxidant and anti-inflammatory effects.	[52, 53]
	Interfere with melanin transfer from melanocytes to keratinocytes.	[9]
	Interferes with intracellular signaling cascades associated with cAMP and CREB. Inhibits CREB phosphorylation, a major transcriptional activator of MITF, thereby reducing MITF transcription and translation.	[50]
Tranexamic acid	Interfere with plasmin-mediated inflammatory pathways in keratinocytes.	[57]
	Inhibition of tyrosinase and depletes the keratinocyte pool or arachidonic acid involved in the UV-induced melanogenesis.	[58]
	Inhibit plasminogen binding receptor.	[59]
	Induce autophagy in melanoma cells by activating signaling pathways such as MAPK/ERK, and increasing the expression of autophagy-related proteins.	[60]
Phytochemicals	Inhibit tyrosinase activity, suppress melanogenesis-related signaling pathways, and provide antioxidant effects that reduce oxidative stress involved in melanin production.	[67 – 69]
Microbiota Metabolite	Propionic acid from *C. acne* reduces UVB-induced melanin synthesis by binding to FFAR2, directly suppressing tyrosinase activity without disrupting melanocyte proliferation.	[64]
	Cyclo (L-Pro-L-Tyr) from *C. tuberculostearicum* enters the substrate pocket of tyrosinase to inhibit enzyme activity.	[65]
	B. longum Strain ZJ1 ferments decrease α-MSH-induced melanin upregulation and reduce intracellular tyrosinase activity.	[66]

4. Nanotechnology-Based Delivery Systems for Hyperpigmentation

4.1. Lipid-Based Nanocarriers

Liposomes are vesicles that are typically spherical in shape, composed of one or more phospholipid bilayers surrounding an aqueous core. This unique amphiphilic structure mimics the biological membranes, which allow liposome to encapsulate various hydrophilic compounds in aqueous compartment and various hydrophobic compounds in amphiphilic lipid layer. Therefore, this structure makes liposome an excellent carrier for drug delivery and other applications [70].

Liposomes are classified based on several structural and compositional parameters. A primary classification is according to their size and number of bilayers. Multilamellar vesicles (MLVs) are usually large and heterogenous structures with multiple concentric lipid layers. Followed by large unilamellar vesicles (LUVs) and small unilamellar vesicles (SUVs) possess

a single bilayer with dimeter ranging from 100 – 1000 nm and 20 – 100 nm respectively [70, 71]. Another critical classification is based on the surface charges, which are cationic, anionic or neutral liposomes. These charges could significantly influence their interaction with biological systems. Furthermore, the advancement has led to more complex development in liposomes such as stealth liposomes which are coated with polymers to evade immune system detection and prolong the circulation time, and ligand-targeted liposomes which are surface-modified with antibodies or peptides for active targeting to specific cells or tissues [71]. Table 2 shows the summary of classification of liposomes.

Table 2. Classification and types of liposomes.

Classification	Types	Descriptions	Citations
Structural/ Lamellarity	Small unilamellar vesicles (SUV)	Size of liposome usually range from 10 – 100 nm. Contains a single lipid bilayer enclosing with an aqueous core. Ideal for drug encapsulation.	[70, 71]
	Large unilamellar vesicles (LUV)	Size usually ranges from 100 – 500 nm. Has a larger single bilayer which comes with a higher entrapment than SUVs.	
	Giant unilamellar vesicles (GUV)	Size is usually more than 1000 nm. It consists of single bilayer and its large size, which is more suitable for cell mimicry studies.	
	Multilamellar vesicles (MLV)	Size is above 500 nm. Consists multiple bilayers which look like an onion-like layer. High lipid content, usually used in cosmetics.	
	Oligolamella vesicles (OLV)	Consists of 2 – 5 bilayers which size ranging from 5 – 100 μm. This is an intermediate form of multilamellar.	
	Multivesicular vesicles (MVV)	It comes in different sizes as it contains a single outer lipid layer with multiple inner vesicles. Usually use for sustained release studies.	
Charged	Neutral charged phospholipids	Basic self-assembly, no surface modification. It is simpler in structure and biocompatible. Encapsulates both hydrophilic and hydrophobic drugs.	[70]
	Positively charged phospholipids	Usually have charges between +15 to +60 mV. For cosmetic and DNA/ RNA target drugs.	
	Negatively charged phospholipids	Usually between -15 to -60 mV. For topical delivery.	
Advanced liposome	Long-circulating (Stealth)	PEGylated lipids such as PEG-DSPE coating phospholipids. Steric stabilization reduces opsonization and REC clearance. Prolonged blood-circulation and reduced immunogenicity. Immunotherapy or cancer drug applications.	[70]
	Targeted/ Ligand-conjugated	Has ligands like antibodies and peptides on the phospholipid surfaces. It is released through a specific binding receptor. For oncology and immunotherapy application.	[73]
	pH-sensitive	Phospholipids membrane destabilized in acidic environment. Usually for intracellular drug release or to escape the lysosomes.	[74,75]

		Example fusogenic lipid like DOPE with CHEMS. For anti-cancer drug application.	
	Stimuli-responsive	Disruption of bilayers due to external or internal trigger. On-demand release. For photodynamic and diagnostic application.	[76]
	Immunoliposome	Contains antibodies coated phospholipids. It is antigen specific targeting which can precisely target immune cell engagement. For targeted immunotherapy.	[77]

Study by Wu et al [78] showed that encapsulation of hydroquinone in NLC could enhance the stability against oxidation and improve skin penetration. The study was done through Franz cell transdermal diffusion study where artificial skin membrane was used. Throughout the study, the result showed NLC encapsulated hydroquinone penetration was better than hydroquinone alone. The study also supported that NLC encapsulated hydroquinone was better than hydroquinone when treated for anti-pigmentation. The tyrosinase assay was done after the exposure to UVA and UVB, and NLC encapsulated hydroquinone showed a good inhibition at 42.39 ± 0.63 % compared to hydroquinone alone which was at 28.40 ± 1.12 %. Another article from Hwang et al [79] also showed good anti-pigmentation by having anthocyanin encapsulate in liposome. In his study, DPPH scavenging activity of liposomal anthocyanin was at 76% at 50 mg/mL compared to anthocyanin alone (24% at 50 mg/mL). Not only that, the inhibition on melanin production was also doubled up for liposomal anthocyanin which is at 60% at 50 mg/mL. In short, liposomal encapsulation not only increases the stability of the anti-pigmentation compound but also increases the efficacy of the treatment.

4.2. Polymeric Nanocarriers

The polymeric nanoparticles are a class of nanocarriers composed of biodegradable and biocompatible polymers that form solid colloidal particles ranging approximately from 10–1000 nm [80]. They can be either in nanospheres or nanocapsules, which nanospheres having an active compound incorporated throughout the polymeric matrix and nanocapsules encapsulated the active compound within the polymeric shell. In the context of anti-hyperpigmentation treatment, polymeric nanoparticles have been studied and explored for their enhancing dermal penetration, stability and controlled release of topical application of depigmentation agents like kojic acid, arbutin and such [54]. Unlike conventional formulations, polymeric nanoparticles can modulate the drug diffusion via polymer swelling, controlled hydration, enzymatic cleavage or diffusion mechanisms, thereby extending residence time within the epidermis and enhancing depigmenting efficacy [80].

In a study by Omidi *et al*. [81], a cross-linking gelation method combined with ultrasound was employed to create arbutin-incorporated chitosan (AIC) nanoparticles. The cytotoxicity and animal study were done. The cytotoxicity test of AIC was lowered when treated in HFF cell line compared to kojic acid and arbutin alone and was supported by animal test adopting Wistar rats as model that showed no signs of sensitivity after treatment. Besides, the anti-melanogenesis activity has also been evaluated and result showed more effective compared to arbutin and kojic acid alone. Other than that, Saeedi *et al*. [47] also developed a polymeric nanoparticle consisted of kojic acid loaded chitosan and collagen nanoparticles (KA-CSCN-NP) through ionic gelation and ultrasonic preparation. The skin permeability test showed the sample delivered more kojic acid to the dermal layers compared to kojic acid alone. This result had successfully overcome the challenges of kojic acid which are hydrophilic that has penetration limitation when develop as topical products. Besides, dermal irritation test was also conducted on Wistar rats and showed no irritation, which supported by cell cytotoxicity test as well. Lastly, the research also performed anti-melanogenic test and showed that KA-CSCN-NP was significantly inhibited L-dopa auto-oxidation by 94.80 ± 2.41 % compared to pure kojic acid solution at 75.28 ± 3.22 %. Hence, through developing anti-pigmentation agents in polymeric nanoparticles can enhance the efficacy and lower the toxicity for a safer options as anti-hyperpigmentation treatment.

4.3. Inorganic Nanocarriers

The nanocarriers of non-metal elements like sulphur and diamonds are being researched to be used for drug delivery to treat hyperpigmentation [80]. The inorganic nanocarriers can be categorized into with metallic elements and with non-metallic elements. The non-metallic element like diamond and sulphur are encapsulated within the core, while metals are encapsulated within the shell to provide a substrate for conjugation with bio-macromolecules. Unlike organic lipid-based systems, inorganic nanocarriers such as metallic nanoparticles, mesoporous silica nanoparticles, and clay-based nanostructures exhibit superior physicochemical stability, tunable surface chemistry, and controlled-release capabilities. The advantages of using inorganic nanocarriers include providing a high mechanical strength, high chemical stability, and controlled drug release through topical application. The types of inorganic nanocarriers are fullerenes, carbon nanotubes, iron oxide nanoparticles, gold nanoparticles, silver nanoparticles, and quantum dots [80].

In research performed by Kandil *et al*. [82], silica coated zinc oxide (ZnO) nanoparticle was combined with magnesium ascorpyl phosphate (MAP) nanovesicle to treat the mice exposed to UV irradiation. In this research, study found that the expression of

proinflammatory cytokines NK-κB was reduced and silica masked the toxicity of ZnO causing lesser toxicity. When compared with silica coated ZnO alone, both showed significant effects in decreasing the melanin level, roughness index and wrinkles depth with higher effect for the combination. Besides that, Yuniarti *et al*. [83] also conducted a study to investigate the gold nanoparticles encapsulated banana peel extraction. The tyrosinase test was conducted through B16 cells showed a good tyrosinase inhibition and increase in concentration of IL-1β which suggests that banana peel extract loaded in gold nanoparticle have significant potential as anti-hyperpigmentation.

4.4. Nanoemulsions and Microemulsions

Microemulsion are homogenous, transparent, thermodynamic and stable dispersions nanoparticle. The droplet diameter usually ranges from 10–100 nm in which the surfactant coating serves as the barrier between oil and water phases [80]. Microemulsion possesses the ability to transport hydrophilic as well as lipophilic drug molecules as liquid membrane carriers. Microemulsion possesses the ability to enhance the rate of moisturizing chemicals or substances absorption into the skin. Microemulsion has the potential to enhance the permeation of the drug into deeper layers of the skin by disrupting the organized structures of the lipid of the stratum corneum, thereby causing the loss of the barrier property of the skin, thus aiding the drug penetration. For instance, arbutin loaded into a microemulsion was developed in a study. Later, the tyrosinase activity was performed by comparing the arbutin extract alone and in nanoemulsion form. The result showed IC_{50} of 0.96 mg in arbutin extraction whereas 6.06 mg in arbutin loaded microemulsion form. Thermodynamic stability of arbutin microemulsion was also investigated through heat-cool cycles, centrifugation and freeze-thaw cycle stress tests, the sample completed the tests with no signs of creaming, phase separation or cracking which suggested for a stable long-term storage [84].

Nanoemulsion is an ultrafine homogenous transparent or translucent oil-in-water or water-in-oil emulsion with the droplet diameter ranging from 20–200 nm. It is stabilized by surfactants. Nanoemulsion can be prepared under high mechanical process of extrusion by mixing the oil phase with the aqueous phase. It can solubilize the lipophilic active compound and aids in the penetration of the active compound into the skin layers by topical applications [80]. In study by Zilles *et al*. [45], nanoemulsion containing rosehip oil and kojic dipalmitate, an esterified form of kojic acid, was developed. The result showed a good antioxidant activity of nanoemulsion containing rosehip oil and kojic dipalmitate through DPPH assay which was at 87.50 ± 0.38% as compared to ascorbic acid, positive control, 91.45 ± 0.75% when compare at the same concentration. Besides, tyrosinase inhibition test was also conducted and

nanoemulsion containing rosehip oil and kojic dipalmitate had achieved approximately 80% iunhibition at concentration of 1 mg/mL, the activity was even stronger than the ascorbic acid alone which inhibition of tyrosinase activity at approximately 60%.

4.5. Microneedles and Advanced Dermal Delivery

The pursuit of improving topical delivery of anti-melanogenic agents has driven significant interest in physical enhancement technologies, with microneedle (MN) systems emerging as a leading strategy to overcome the barrier of stratum corneum [85]. Microneedles, particularly dissolving microneedles arrays (DMNs), provide a minimally invasive technology that temporarily punctures micro-sized channels through the skin, facilitating the direct and targeted delivery of therapeutic agents to the viable epidermis and dermis, where melanocytes reside [86]. This overcomes the rate-limiting step of passive diffusion through intact skin, which is particularly critical for hydrophilic and high molecular weight compounds. The clinical significance of MNs was highlighted in a few study where it carried depigmentation agents for a better effect of treating hyperpigmentation. This technology ensures that a greater percentage of active compound reaches the target site to enhance the efficacy and also minimize the risk of systemic exposure and side effects for prolonged topical applications [87]. The principal types of microneedles used for transdermal and intradermal delivery including solid, coated, dissolving, hollow, and hydrogel-forming microneedles are illustrated in Figure 6.

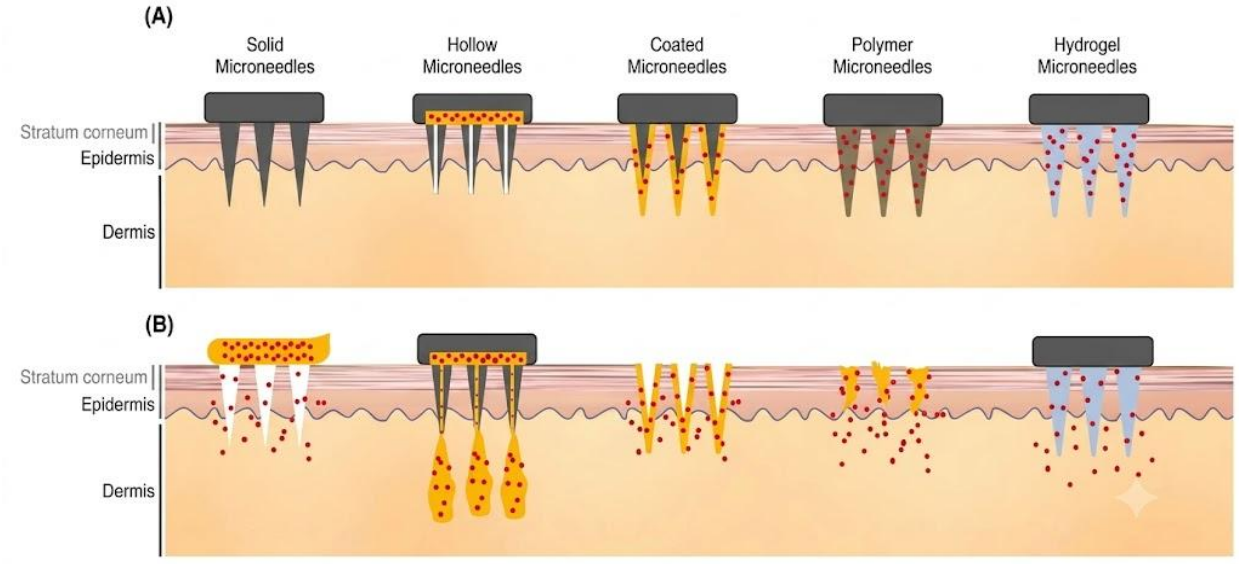

Figure 6. Types of microneedles (Adapted from Wang *et al*., 2021) [88].

MNs can provide dual mechanisms delivery to overcome the limitation in treating hyperpigmentation which are the physicochemical instability, low solubility of the compounds and skin penetration. By using nanocarrier systems, the stability and release of compounds like terpenoids, polyphenols and such from botanical sources are protected and controlled [86, 88]. Subsequently, the nanocarrier system is integrated with a dissolving MN system which provides a dual mechanism in the treatment of hyperpigmentation. The MN physically penetrates the skin and deposits the nanocarrier system upon dissolution, and the nanocarrier system enhances cellular uptake or provides sustained release effects, thereby improving the duration of action.

A compelling example of this advanced combinatorial strategy is the use of dissolving MN incorporating nanocarriers for the delivery of natural tyrosinase inhibitors. For instance, a study by Kitsongsermthon *et al* [86] explored an alternative approach for delivering a depigmenting agent via DMNs, highlighting the feasibility of this platform for natural compounds. Extending this concept, one can envision a system where a natural product like ellagic acid or glabridin, known for its potent tyrosinase inhibition but poor dermal bioavailability, is first encapsulated within lipid-based nanocarriers. These nanocarriers would then be embedded within the matrix of a dissolving microneedle patch. Upon application, the microneedles dissolve in the skin's interstitial fluid, releasing the nanocarriers directly into the microenvironment of the melanocytes. This not only maximizes the localized concentration of the natural anti-melanogenic agent at its site of action but also leverages the nanocarrier to facilitate intracellular delivery, potentially leading to superior and more sustained depigmentation compared to conventional formulations [88]. This integrated approach represents a sophisticated, next-generation strategy for the safe and effective management of hyperpigmentation disorders. Other than that, a comparative study by Quazi *et al*. [89] demonstrated that TXA combining with microneedles was effective in treating for melasma. In this study, patients received three sessions at monthly intervals, with significant improvements in MASI scores on the TXA plus microneedling side.

Other advanced therapy such as chemical peels and laser therapy are also used widely nowadays in treating hyperpigmentation. Chemical peels work by causing desquamation and remove the superficial layer of stratum corneum. It can also combine with other topical agents to enhance the effects [22]. For instance, tretinoin peels have been studied because of their ability to elicit the same therapeutic and histological effects of topical Tretinoin but required a shorter time of treatment. In one study, it has been demonstrated that by increasing the concentration of Tretinoin peels from 1% to 10%, the period of exposure of the skin to the peel has reduced from four to eight hours to just an hour while retaining the same level of

efficacy [90]. In the same way, glycolic acid peels have been proven to be effective in the treatment of hyperpigmentation disorders, including melasma and post-inflammatory hyperpigmentation [91]. Other than that, laser therapy is also an option to most people when considering hyperpigmentation. It uses light amplification by stimulated emission of radiation to reduce the melanin amount. For example, Q-switched neodymium-doped yttrium aluminium garnet laser was used due to its highly selective properties and lesser damage to epidermis layer. This not only reduce the damage to epidermis layer, but according to most studies, it is well absorbed by the melanocytes at low doses making it more effective in depigmentation treatment [22]. Table 3 provides a comparative overview of conventional and advanced delivery systems, highlighting their respective mechanisms, advantages, limitations, and applications in hyperpigmentation treatment.

Table 3. Compare and contrast of conventional and advanced delivery systems.

Category	Dosage Form	Mechanisms of Delivery	Targeting Efficiency	Irritancy / Safety	Key Advantages	Key Limitations
Conventional Formulations	Topical creams or gels	Passive diffusion through stratum corneum	Low, limited by skin barrier [62]	Moderate to high irritation, cytotoxicity and ochronosis risk [2,10]	Easy application, low cost, established efficacy	Poor penetration, instability, high relapse rate [8]
	Chemical peels	Removal of stratum corneum to enhance penetration	Moderate, indirect enhancement [22]	Moderate irritation, risk of erythema	Enhances efficacy of topical agents	Requires supervision, not suitable for all patients
	Oral dosage form	Systemic circulation to melanocytes	Low, limited by hepatic metabolism and gastrointestinal absoprtion	Low, unless serve in high dose	Effective for severe pigmentation	Safety concerns limit long-term use
Nanoparticle-based and Advanced Delivery Systems	Lipid-based nanocarriers	Fusion with stratum corneum lipids and enhanced partitioning into epidermis. Facilitates drug accumulation near melanocytes	Moderate to high due to improved skin permeation [71]	Reduced irritation due to encapsulation and controlled exposure [34]	High biocompatibility, enhances penetration and efficacy, suitable for both hydrophilic and lipophilic drugs	Drug leakage, limited long-term stability, possible surfactant-related irritation
	Polymeric nanoparticles	Controlled and sustained release via diffusion, polymer swelling, or degradation	High, sustained localization near melanocytes [80]	Low cytotoxicity and reduced irritation compared to free agents [47,48]	Superior stability, controlled release, reduced toxicity, enhanced efficacy	Complex formulation, higher production

						cost, scalability challenges.
	Inorganic nanoparticles	Cellular uptake and surface interaction. Allow targeted delivery via surface modification	Moderate to high depending on functionalization [80]	Potential toxicity and accumulation concerns; improved with surface coating [82]	Improve stability, tunable surface properties, strong photoprotective effects	Long-term safety concerns, risk of bioaccumulation, regulatory uncertainty
	Nanoemulsions / Microemulsions	Disruption of stratum corneum lipid structure, enhancing permeation of active compounds	Moderate to high via chemical penetration enhancement [80]	Moderate irritation risk due to surfactants [80]	Improves solubility and bioavailability, easy formulation, good spreadability	Surfactant-induced irritation, limited drug retention in deeper layers
	Microneedles	Physical bypass of stratum corneum via microchannels and controlled release from nanocarrier at target site	Very high, direct delivery to epidermis/dermis where melanocytes reside [62,86]	Low irritation due to localized and controlled delivery; minor infection risk if improperly used [87]	Maximized targeting efficiency, sustained release, reduced systemic exposure [80]	High cost, device dependency, complex manufacturing and regulatory pathway

5. Cellular Uptake and Intracellular Trafficking of Nanocarriers in Hyperpigmentation Therapy

Nanocarriers have presented superior skin penetration performance compared with conventional topical preparation. However, it is important to understand the intracellular delivery mechanism to melanocytes residing within the basal epidermis as well and how this leads to improve in their therapeutic efficacy ultimately. For a successful delivery of active to the targeted site, after the nanocarriers penetrate through the stratum corneum and viable epidermis, they must traverse the epidermal basement membrane, undergo the process of cellular internalization, avoiding premature degradation, and releasing their encapsulated cargo at the appropriate intracellular site. These intracellular trafficking processes largely determine intracellular drug bioavailability and ultimately influence therapeutic efficacy [92,93].

5.1. Transport of Nanocarriers Across the Epidermal Basement Membrane

The epidermal basement membrane is a specialized extracellular matrix in the skin, primarily consist of laminin, collagen IV, nidogen, and perlecan. These compounds form a

layer of highly organized network that separates the epidermis from the dermis while controlling molecular transport across the sin and maintaining tissue integrity [94]. Transportation of nanoparticles across the skin face some steric hindrance due to the dense extracellular matrix unlike low-molecular-weight compounds that can diffuse relatively freely. Their transport depends largely on particle size, surface charge, deformability, and interactions with extracellular matrix proteins [92].

Nanoparticles smaller than approximately 50–100 nm generally are easier to diffuse and penetrate through because their small size enable them to pass through the nanoscale pores and transient intercellular spaces present within the extracellular matrix [95]. Nanoparticles integrated with PEG at the surface further facilitates diffusion by minimizing nonspecific protein adsorption and reducing adhesive interactions with collagen fibres, thereby increasing nanoparticle mobility within biological tissues [96]. In disease state such as inflammatory skin disorders and post-inflammatory hyperpigmentation, elevated expression of matrix metalloproteinases (MMPs) partially disrupts basement membrane architecture, increasing tissue permeability and facilitating nanoparticle migration toward melanocytes located within the basal epidermis [97]. Furthermore, deformable lipid-based nanocarriers such as transfersomes and elastic liposomes can reversibly deform while maintaining membrane integrity, enabling passage through extracellular spaces considerably smaller than their original particle diameter.

5.2. Endocytic Uptake Pathways of Nanocarriers

When nanocarriers reach basal epidermis, they are taken up by keratinocytes and melanocytes through mechanisms such as endocytosis, with the predominant pathway determined by particle size, surface chemistry, composition, and ligand modification [93,98].

Clathrin-mediated endocytosis represents the most extensively characterized uptake mechanism for polymeric nanoparticles, polymeric micelles, dendrimers, and ligand-functionalized nanoparticles generally smaller than 200 nm. During this process, clathrin-coated pits invaginate to form intracellular vesicles that subsequently mature into early endosomes before progressing toward lysosomal compartments [98]. Although this pathway provides highly efficient cellular uptake, exposure to lysosomal enzymes may prematurely degrade sensitive therapeutic molecules.

In contrast, caveolae-mediated endocytosis predominantly takes up lipid-based nanocarriers including liposomes, nanostructured lipid carriers, and cholesterol-rich nanoparticles. Caveolae are flask-shaped plasma membrane invaginations enriched with

cholesterol, sphingolipids, and caveolin-1 proteins. Unlike clathrin-mediated trafficking, caveolae can easily bypass lysosomal degradation and transport cargo toward caveosomes, the Golgi apparatus, or endoplasmic reticulum, thereby preserving drug stability and increasing intracellular bioavailability [99]. Consequently, caveolae-mediated uptake is considered particularly advantageous for delivering nucleic acids, peptides, proteins, and oxidation-sensitive depigmenting agents.

Besides these classical mechanisms, larger nanoparticles and positively charged formulations may also undergo macropinocytosis or lipid raft-mediated endocytosis through actin-dependent membrane ruffling, thereby expanding intracellular delivery pathways available to nanocarrier systems.

5.3. Lysosomal Processing and Intracellular Drug Release

Lysosomes are acidic intracellular organelles (pH 4.5–5.0) containing numerous hydrolytic enzymes including proteases, lipases, glycosidases, and esterases. Before arriving at the lysosomes, nanoparticles are sequentially transported from early endosomes to late endosomes [100].

In the lysosomes, the shell of the biodegradable polymeric nanoparticles formed from polymers such as poly(lactic-co-glycolic acid) (PLGA) or chitosan undergo gradual hydrolysis or enzymatic degradation. This leads to controlled intracellular release of encapsulated therapeutic agents [101]. Likewise, pH-responsive liposomes are engineered to destabilize under acidic lysosomal conditions, thereby promoting membrane fusion and intracellular drug release.

However, it should be noted that excessive lysosomal degradation may reduce therapeutic efficacy due to premature destruction of encapsulated bioactive compounds. To overcome this limitation, many advanced nanocarriers are engineered to incorporate endosomal escape mechanisms, including proton sponge polymers such as polyethyleneimine, fusogenic lipids, and pH-sensitive polymers capable of destabilizing endosomal membranes before lysosomal maturation [102]. These strategies enable therapeutic molecules to enter the cytoplasm, where they effectively inhibit MITF signalling, suppress tyrosinase activity, and regulate oxidative stress pathways involved in melanogenesis.

5.4. Transcytosis in Keratinocyte–Melanocyte Communication

There are growing evidences indicating that transcytosis provides an additional mechanism by which nanocarriers traverse the epidermis while maintaining structural

integrity. During the transcytosis process, nanoparticles are taken up at the apical membrane of keratinocytes, transported intracellularly within vesicular compartments, and subsequently exocytosed through the basal membrane without extensive lysosomal degradation.

Within the epidermal melanin unit, keratinocytes and melanocytes continuously exchange cytokines, extracellular vesicles, melanosomes, and regulatory proteins that coordinate melanogenesis. Nanocarriers capable of exploiting transcytotic pathways may therefore facilitate targeted delivery of depigmenting agents directly to melanocytes while simultaneously modulating keratinocyte-derived paracrine mediators including α-MSH, endothelin-1, stem cell factor, and inflammatory cytokines that regulate melanin synthesis [103].

Furthermore, increasing evidence suggests that engineered extracellular vesicles and biomimetic nanoparticles may exploit endogenous intercellular communication pathways to enhance selective melanocyte targeting while minimizing off-target drug accumulation [104]. Such biomimetic delivery systems represent an emerging strategy for next-generation nanocosmeceutical therapies against hyperpigmentation.

6. Clinical Insights and Translational Relevance

6.1. Preclinical and Clinical Evidence

The transition of nanotechnology from research to clinical application has proven to be highly efficient in the management of hyperpigmentation. The translational journey of nanotechnology-based formulations from the laboratory to clinical application is supported by a growing body of preclinical and clinical evidence demonstrating their superiority over conventional therapies for hyperpigmentation. In-vitro studies have consistently shown that encapsulation of depigmenting agents within nanocarriers significantly enhances their anti-melanogenic efficacy. For instance, hydroquinone- loaded NLCs demonstrated a tyrosinase inhibition rate of 42.39 ± 0.63% in B16 melanoma cells following UV exposure, which was markedly higher than the 28.40 ± 1.12% inhibition achieved by free hydroquinone, illustrating the benefit of improved stability and targeted delivery [78]. Similarly, polymeric nanoparticles have addressed the longstanding challenge of hydrophilic compound penetration; kojic acid-loaded chitosan-collagen nanoparticles facilitated greater dermal delivery and achieved a 94.80 ± 2.41% inhibition of L-dopa auto-oxidation, compared to 75.28 ± 3.22% for a pure kojic acid solution [47]. These findings underscore the capacity of nanocarriers to potentiate the activity of both synthetic and natural anti-pigmenting agents.

Apart from in-vitro models, in-vivo and clinical studies are validating the practical advantages of these advanced delivery systems. The use of physical enhancement technologies, such as DMNs, has shown particular promise in clinical settings. By creating transient microchannels that bypass the stratum corneum, DMNs ensure that a greater proportion of the active compound reaches the basal layer where melanocytes reside, directly addressing the chronic and recurrent nature of conditions like melasma [87]. Clinical studies have confirmed that DMNs armed with anti-melanogenic compounds can achieve significant and uniform depigmentation, with the added benefit of enhanced patient compliance due to the painless and self-administrable nature of the platform [62,86]. The clinical outcome is not merely enhanced skin lightening but also a potential reduction in relapse rates, as the sustained release properties of integrated nanocarrier-microneedle systems can maintain therapeutic levels at the target site over an extended period [88]. This body of evidence collectively confirms that nanotechnology is transitioning from a theoretical concept to a clinically relevant strategy for improving patient outcomes in hyperpigmentation therapy.

6.2. Safety Considerations

A primary driver for adopting nanotechnology in cosmeceuticals is the reduction of skin irritation associated with conventional high-dose topicals. By encapsulating potent but irritant compounds within a biocompatible shell, nanocarriers can modulate drug release and minimize direct contact with the skin surface, thereby improving the overall safety profile. This principle is well-illustrated by studies on polymeric nanoparticles. Arbutin-incorporated chitosan nanoparticles demonstrated lower cytotoxicity in HFF cell lines and showed no signs of dermal sensitivity in Wistar rat models compared to pure arbutin or kojic acid, confirming a safer alternative for sensitive skin [81]. Likewise, kojic acid-loaded chitosan-collagen nanoparticles not only enhanced efficacy but also passed dermal irritation tests in animal models, reinforcing that encapsulation can decouple efficacy from irritancy [47].

However, the field should address nanotoxicity with care, especially regarding non-biodegradable materials. While inorganic nanocarriers have shown greater physicochemical stability, the problem of long-term retention in the dermis remains. On the molecular level, the continuous presence of such nanoparticles may cause toxicity through various mechanisms. One of these is the oxidative stress caused by nanoparticles, wherein the large surface area of the inorganic core causes an increase in catalysis of ROS production, leading to the breakdown of cellular defenses and consequently resulting in the oxidation of lipids, formation of protein carbonyls, and mitochondrial dysfunction. Moreover, some crystalline nanoparticles could destabilize the lysosome after internalization by the cells. As a

consequence, the disruption of the lysosomal membrane leads to the release of cathepsin B into the cytoplasm and activates the NLRP3 inflammasome pathway and production of ILs [105, 106].

Aside from direct inflammatory mechanisms, prolonged exposure to low doses of nanoparticles raises the risk of genotoxicity. Thus, thorough safety measures should include DNA damage detection methods through the application of the alkaline comet assay technique for the identification of single and double-strand DNA breaks as well as the measurement of γ-H2AX focus counts via immunofluorescence to provide a highly sensitive indicator of double-strand DNA damage and impaired genomic integrity [107,108]. Moreover, nanoparticle buildup under sub-toxic conditions is capable of producing a number of epigenetic alterations, including the dysregulation of miRNAs. Non-coding RNA profile alteration can affect downstream gene networks responsible for epidermal cell differentiation and tissue repair in addition to melanocytes maintenance [108].

New approaches, such as using biocompatible coatings for potentially toxic metallic nanoparticles, have been investigated to resolve the problem. For example, silica-coated zinc oxide nanoparticles were successfully combined with vitamin C nanovesicles to reduce the expression of proinflammatory cytokines. This effectively masks the native toxicity of the metallic nanoparticle while retaining the photoprotective and depigmenting effects of the compound [82]. This is a major problem because the potential for chronic low-level toxicity from non-biodegradable particles is a major concern. Therefore, the continued development of nanocosmeceuticals should be paralleled by the development of regulatory sciences to ensure that these new tools provide a therapeutic benefit while avoiding unforeseen health risks.

6.3. Regulatory Perspectives

The regulatory landscape for nanocosmeceuticals is complex, often blurring the lines between cosmetic and drug classifications. One of the challenges is how to classify nanocosmeceuticals, as their mode of action, which involves crossing the dermal barrier to affect physiological processes such as tyrosinase activity, blurs the distinction between a cosmetic and a drug. Although an active ingredient may be cleared for certain purposes, its formulation with a new nanotechnology-based system could affect its bioavailability and activity, which could subject it to more rigorous testing than a typical cosmetic [87]. For example, a dissolving microneedle patch containing an anti-melanogenic compound is more than an application of a topical active ingredient, as it is a device-based approach to delivery, which could require a different regulatory approach than a topical cream [62].

Currently, there is a recognized lack of globally standardized safety regulations specifically tailored for nanomaterials used in the cosmetic industry. This regulatory gap presents a significant hurdle for manufacturers seeking to introduce innovative products like natural product-loaded nanocarriers combined with microneedle systems [88]. Questions remain regarding the appropriate methodologies for assessing long-term dermal exposure, potential systemic absorption, and the environmental impact of these materials. The establishment of clear, science-based global standards is therefore essential. Such frameworks would not only ensure consumer safety by mandating rigorous toxicological assessments but also provide a predictable pathway for innovation, encouraging the development of advanced formulations that can deliver consistent therapeutic benefits without unforeseen health risks.

6.4. Market and Consumer Acceptance

Despite regulatory complexities, the market for advanced dermatological and cosmeceutical products is robust and increasingly driven by consumer demand for safer, more effective, and scientifically validated solutions. The limitations of conventional therapies like skin irritation from hydroquinone or the poor efficacy of some natural compounds due to stability issues, have primed consumers to seek out next-generation alternatives [10, 22]. Nanotechnology-based formulations address these very pain points by offering the promise of enhanced efficacy with a superior safety profile, as demonstrated by the reduced cytotoxicity of arbutin-loaded chitosan nanoparticles compared to their free-form counterparts [81]. This alignment with consumer desires for biodegradable but potent skincare positions nanocosmeceuticals favorably in the market.

Furthermore, consumer acceptance is also boosted by the convenience and patient-centric nature of some of these advanced delivery systems. The introduction of painless, easy-to-use dissolving microneedle patches, for instance, meets the increasing demand for at-home, self-administerable treatments that provide clinical-level results [86]. This delivery system does not only provide better results by going beyond the skin's stratum corneum but also provides a better consumer experience, which is a major factor in ensuring adherence in the management of chronic conditions such as melasma. As consumers continue to become more educated in skincare science, the popularity of delivery systems that combine natural extracts with nanotechnology for better penetration is expected to continue increasing [88]. However, the success of these delivery systems in the market will depend on the effectiveness of communicating their benefits to consumers, as well as the clinical validation of their superiority to ensure consumer trust.

6.5. Skin Microbiome Implications of Topical Nanoformulations

Skin microbiome plays a key role in epidermal barrier function, local immune responses and prevention of pathogen colonization. With previous discussed on the topical nanocosmeceutics in anti-pigmentation, it provides positive and negative effects towards the skin microbiome. Conventional topical formulations usually required higher concentration of active ingredients to carry depigmentation effects as they need to overcome the skin barrier. The abrupt flooding of the stratum corneum can alter the microenvironment on skin, therefore create a harsh antimicrobial pressure that indiscriminately wipe out the normal flora species like *S. epidermidis*. As discussed above, disturbances in the microbial balance may influence the activity of *C. acnes*, whose porphyrin metabolites can generate ROS when exposed to UV and promote melanogenesis [27]. Nanoparticles could encapsulate these actives compounds, releasing them in a controlled, sustained manner [70,78]. This limits the concentration of the active ingredient on the skin surface, safeguarding the baseline microbial community from chemical-induced dysbiosis.

On the other hand, due to different physicochemical properties of each active ingredients, excipients used to stabilize the nanoformulations can directly interact with the microbial membrane. Some excipients such as surfactant used in microemulsion and nanoemulsion might possess non-specific antimicrobial activities or alter the sebum composition that skin commensals rely on the lipid metabolism [80]. Some inorganic nanoparticles particularly metallic nanoparticles required careful optimisation as liberation of free metal could exert antimicrobial effects causing severe structural collapse of the native microbiome. Hence, more study scope should cover to understand overall nanoformulations effects towards the skin environment. Besides, bio-based polymers like alginate or chitosan could be introduce due to due to its excellent biocompatibility with skin microorganisms and stability in formulations.

6.5.1. Molecular Crosstalk Between Skin Commensals and Melanocytes

The skin microbiome has been studied extensively and recognized for its role in regulating cutaneous homeostasis through continuous interactions with keratinocytes, immune cells, and the epidermal barrier. The causal relationship might not be direct, instead commensal microorganisms primarily influence pigmentation indirectly by modulating inflammatory responses, oxidative stress, and barrier integrity. Microbial-derived molecules can stimulate keratinocytes to produce cytokines, antimicrobial peptides, ET-1, stem cell factor (SCF), and α-MSH, which subsequently activate melanocyte signalling pathways involving cAMP, MITF, and tyrosinase, ultimately promoting melanogenesis [109, 110].

Furthermore, any disruption of the skin microbial ecosystem has been linked to persistent cutaneous inflammation, increased oxidative stress, and impaired epidermal barrier function, all of which may contribute to the development or persistence of pigmentary disorders such as post-inflammatory hyperpigmentation [109, 110]. Although there are insufficient direct evidence linking individual commensal species with melanocyte regulation, but the emerging understanding of host–microbiome interactions suggests that maintenance of microbial homeostasis may indirectly influence skin pigmentation.

6.5.2. Nanocarrier–Microbiome Interactions

Besides enhancing topical drug delivery, nanocarrier systems may have an effect on the skin microbiome by altering the physicochemical environment at the skin surface. Factors such as hydration, lipid organization, pH, and local antimicrobial activity may affect microbial composition and metabolic function. For example, metallic nanoparticles, particularly silver nanoparticles, exhibiting broad-spectrum antimicrobial properties might reduce bacterial colonization and biofilm formation on the skin. In contrast, lipid-based and polymeric nanocarriers generally have more neutral effect on skin microbiome and demonstrating greater biocompatibility and are less likely to disrupt resident commensal microorganisms. However, the evidence regarding the long-term effects of topical nanocarriers on skin microbial ecology remains scarce, and preservation of beneficial microbial communities should be considered during formulation development. Future nanocosmeceutical design should therefore balance enhanced drug delivery with maintenance of microbial homeostasis [109, 110].

6.5.3. Postbiotic Compounds as Emerging Anti-Melanogenic Agents

Postbiotics, an emerging research area, defined as preparations of inanimate microorganisms and/or their metabolites that confer health benefits, which are promising cosmetic ingredients owing to their excellent formulation stability and favourable safety profile compared with live probiotics. Current research evidence indicates that postbiotic metabolites may improve skin barrier function, reduce oxidative stress, and suppress inflammatory signalling, thereby creating a cutaneous microenvironment that is less conducive to excessive melanogenesis. For instance, phenyllactic acid (PLA) is a metabolite produced by probiotic bacteria that showed tyrosinase inhibition through supressing melanin synthesis [111]. Although there are currently limited studies directly evaluating postbiotics as anti-melanogenic agents, recent findings have strengthened their therapeutic potential. For example, Chang *et al.* [112] demonstrated that postbiotics derived from *Pediococcus acidilactici* LS significantly inhibited melanogenesis while simultaneously providing

photoprotective, antioxidant, and wound-healing activities. This suggests that postbiotics may target multiple pathological mechanisms involved in hyperpigmentation. Furthermore, accumulating evidence indicates that postbiotic metabolites, including short-chain fatty acids, exopolysaccharides, bacteriocins, and organic acids, can modulate oxidative stress and inflammatory pathways that are closely associated with UV-induced melanogenesis and pigment dysregulation [112]. Their antioxidant and immunomodulatory properties suggest considerable potential as adjunctive ingredients for hyperpigmentation management. Incorporation of postbiotic-derived bioactive molecules into nanocarrier systems may further enhance their stability, controlled release, and penetration into the viable epidermis, representing an emerging direction for future nanocosmeceutical development [113].

6.5.4. Prebiotic Strategies for Modulating Skin Microbiota

Prebiotics are selectively utilized substrates that can promote growth and metabolic activity of beneficial microorganisms while suppressing microbial dysbiosis. In dermatology, prebiotic have been studied for its potential to improve epidermal barrier integrity, regulating immune responses, and restoring microbial balance rather than directly inhibiting melanogenesis. Nevertheless, because chronic inflammation and oxidative stress contribute significantly to persistent pigmentation disorders, restoration of a healthy skin microbiome may indirectly reduce melanocyte activation and melanin synthesis. Future nanotechnology-based formulations capable of co-delivering depigmenting agents together with microbiome-modulating ingredients may therefore provide synergistic therapeutic benefits by simultaneously targeting melanogenesis and maintaining microbial homeostasis [110].

6.5.5. Safety Assessment of Nanoformulations on Skin Microbial Diversity

As microbiome-friendly cosmetic formulations continue to emerge, evaluation of their long-term effects on skin microbial diversity has become increasingly important. High-throughput 16S rRNA gene sequencing, metagenomic sequencing, and other multi-omics technologies are now widely employed to characterize microbial richness, diversity, and taxonomic composition following topical treatment. These approaches enable comprehensive assessment of whether nanoformulations selectively preserve beneficial commensal microorganisms while minimizing undesirable microbial dysbiosis. Integration of microbiome profiling into nanocosmeceutical safety evaluation may therefore complement conventional dermatological assessments and provide a more comprehensive understanding of formulation safety and long-term skin health [110, 113].

7. Challenges and Future Perspectives

Despite the considerable promise of nanotechnology-based interventions for hyperpigmentation, there are several challenges that need to be addressed. The most critical of these is lack of standardized, globally harmonized safety regulations that are specific to the application of nanotechnology-based interventions. This has been discussed under the regulatory considerations, where the ambiguity with regards to the classification of these interventions, i.e., whether they fall under cosmetics or drugs, has raised several critical issues with regards to long-term consumer safety [87]. This is particularly applicable with regards to the application of inorganic nanocarriers, where there are several critical issues with regards to the long-term accumulation of non-biodegradable material in the dermis, which needs to be addressed through the development of universally accepted protocols for nanotoxicity [80, 82].

Moreover, there is an urgent need to establish robust and long-term clinical data and comparative studies. In vitro and short-term in vivo studies have shown the improved efficacy and reduced irritation potential of nanocarrier systems, such as arbutin-loaded chitosan nanoparticles [81] and kojic acid-loaded polymeric nanoparticles [47]. However, their relative efficacy to established gold-standard treatments during long-term studies remains under investigated. This is not only important to obtain approval for these treatments but also to establish trust among clinicians and consumers who wish to be assured of the long-term benefit and safety of these treatments. We should move beyond the proof-of-concept stage to obtain the data required to inform evidence-based practice.

Looking forward, the future of hyperpigmentation therapy lies in the convergence of advanced delivery technologies with personalized medicine and sustainable sourcing. A particularly exciting avenue is the integration of nanotechnology with artificial intelligence (AI) and advanced computational modeling to develop personalized skincare regimens. Specifically, researchers can now utilize deep learning for high accurate skin phenotype classification, machine learning algorithms for predicting complex nanoparticle-melanocyte interactions, and molecular dynamics simulations to elucidate the exact mechanisms of nanocarrier-membrane fusion. AI-driven analysis of individual skin characteristics, melanin distribution, and genetic predispositions could guide the rational design of customized nanocarrier formulations, ensuring that the right combination of active agents is delivered to the right target at the optimal dose. AI-assisted formulation optimization and digital dermatology platforms may also accelerate clinical decision-making, improve treatment

efficacy, and reduce unnecessary formulation development costs by enabling predictive screening of nanocarrier performance prior to experimental validation.

To truly realize the potential of personalized medicine, these platforms must integrate specific molecular biomarkers. Key strategies include utilizing MC1R genotyping to accurately predict patient response, monitoring MITF expression levels as reliable pharmacodynamic marker, and incorporating skin microbiome typing to tailor formulations to the host microenvironment. Future research can also prioritize the development of advanced, targeted nanoparticle delivery systems that can precisely home to cutaneous melanocytes or their stem cell niches following topical or intradermal administration, thereby avoiding off-target editing in other skin cells. Furthermore, as CRISPR-Cas9 delivery via nanoparticles for permanent pigmentation disorder correction moves toward the clinic, significant efforts are required to engineer Cas9 variants with ultra-high fidelity and to develop transient delivery strategies that minimize the risk of immunogenicity and prolonged genomic exposure. As CRISPR-Cas9 delivery via nanoparticles advances toward clinical translation, its successful implementation will also depend on robust regulatory oversight and ethical governance. This includes comprehensive evaluation of off-target genome editing, long-term safety monitoring, transparent informed consent, equitable access to therapy, and adherence to evolving international regulatory frameworks for human gene-editing technologies. Finally, alongside refining the delivery vehicle, establishing long-term safety profiles in large animal models, assessing the stability of the repigmentation phenotype over decades, and developing combinatorial delivery of base editors or epigenetic modulators will be essential to address the heterogeneous genetic causes of these disorders and ensure a durable, naturalistic cosmetic outcome. Despite these promising advances, the broad clinical application of AI-based personalized nanomedicine and CRISPR technology-based treatment options would also require better cost-efficiency, scalability of production, and accessibility. Such considerations will be necessary in order to ensure that next-generation hyperpigmentation treatments are not only innovative from a scientific perspective but can also be clinically feasible to patients.

Last but not least, the opportunities presented by natural product-loaded nanocarriers are vast and remain a fertile ground for innovation. Botanical compounds such as ellagic acid, glabridin, and hesperidin offer potent tyrosinase inhibitory activity but are often hampered by poor solubility and stability [67, 88]. By encapsulating these phytochemicals within lipid-based or polymeric nanocarriers and further integrating them into advanced delivery platforms like dissolving microneedles, researchers can create sophisticated, multi-functional systems that maximize efficacy while minimizing systemic exposure [86]. This synergistic approach not

only harnesses the therapeutic potential of nature but also addresses the physicochemical limitations that have historically hindered the clinical translation of natural products, paving the way for a new generation of safe, effective, and sustainable hyperpigmentation therapies.

8. Conclusion

In summary, nanotechnology enables precise molecular intervention in the melanogenesis cascade, from tyrosinase inhibition to MITF silencing, while preserving skin microbial ecology. The convergence of nanodelivery systems with molecular diagnostics (e.g., MC1R genotyping) and microbiome modulation represents a paradigm shift from empirical depigmentation to mechanism-based precision therapy. The ability of nanocarrier in enhancing skin penetration, active compound stability and targeted delivery, represents a significant leap forward in the precision management of hyperpigmentation and PIH [54]. The clinical translation of these innovations is supported by preclinical evidence as well as emerging clinical data from advanced platforms such as DMNs that demonstrate tangible patients benefits. The novelty of the review lies in between the nanotechnology-based and advanced delivery system and depigmentation agents. By evaluating at the most recent advances and regulatory issues, it gives a plan for making the next generation of cosmeceuticals that work better and safer for long-term clinical use.

However, the key to the successful integration of these technologies into routine clinical practice is a fine balance between innovation and safety. As the formulations get more complex, the need for rigorous long-term toxicological evaluations and the development of a well-defined global regulatory landscape is more pertinent than ever. The road forward is going to need a holistic approach to research that encourages the integration of formulation scientists, clinicians, toxicologists, and regulators. By confronting these challenges head-on and capitalizing on the opportunities that the future holds for personalized AI-based skincare and natural product-based delivery systems, the potential of nanocosmeceuticals is set to be maximized. Ultimately, this will lead to a safer, more efficacious and patient-centred therapies that significantly improved the quality of life for individuals affected by hyperpigmentation worldwide.

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