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Review Article

Recent Advances in the Formulation of Topical Creams for Hyperpigmentation Treatment

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Abstract

The dermatological disease known as hyperpigmentation of the skin causes the skin to become darker or discolored. Treatments for hyperpigmentation problems frequently have low patient compliance and take a very long time to show benefits. Oral formulations of therapeutic agents including tranexamic acid, melatonin, and cysteamine hydrochloride are administered after topical formulations of traditional agents like hydroquinone, kojic acid, and glycolic acid as the first line of treatment for hyperpigmentation. Chemical peels and laser therapy are second-line methods that are administered under the supervision of qualified specialists. Nevertheless, these treatments have drawbacks and side effects such erythema, skin peeling, and dryness, and they take a long time to start showing results. These drawbacks of the traditional therapies opened the door for more investigation into more recent approaches to hyperpigmentation management. Novel formulations include phytochemicals, liposomes, platelet-rich plasma, solid lipid nanocarriers, and microneedling are a few of these treatments. Several hyperpigmentation problems and their processes, as well as new and developing therapeutic approaches for managing hyperpigmentation, are the main topics of this review.

Keywords: Pigmentation; Medication; Microneedling

Introduction

The primary goal of numerous medications and therapeutic-based products has been to achieve an aesthetically attractive skin pigmentation appearance. *Spirulina platensis* contains phycocyanin, a phycobiliprotein, an essential pigment that is used as a dietary supplement in many nations. Due to its low cost, the commercialization of spirulina for its valuable components—such as various proteins and vitamins—is presently taking place in several locations.

In the first two sequential phases of melanin manufacture, tyrosinase, an essential enzyme, catalyzes the hydroxylation of L-tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and the oxidation of DOPA to dopaquinone, which then spontaneously polymerizes to produce melanin. Tyrosinase overexpression encourages the formation of too much melanin, which leads to hyperpigmentation symptoms such age spots, acanthosis nigricans melasma, cervical poikiloderma, and non-melanoma skin cancer. Melanosome-specific regulatory glycoproteins released in coated vesicles from the Golgi apparatus combine with structural proteins secreted from the endoplasmic reticulum during this bipartite process of melanin production.

Many pigmentation problems are caused by either excessive or insufficient melanin production. An essential defense system of the human body, pigmentation guards against UV rays and oxidative stress. However, excessive skin pigmentation is a cosmetic concern. Research is being done on novel low molecular weight peptides that

control skin pigmentation. Phycocyanin from *S. platensis* was digested *in-silico*, resulting in the creation of an internal library of peptides that were subsequently examined for anti-melanogenic properties [7]. A good antioxidant and light-harvesting protein, phycocyanin has been shown to have possible tyrosinase inhibiting qualities.

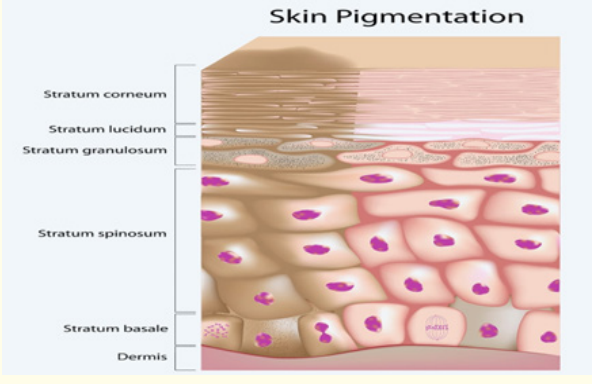

Figure 1

Pathophysiology of hyperpigmentation

Neural crest cells are used to produce melanocytes, which give skin its tegument color. They are cells in the basal layer at the dermal and epidermal junction that produce melanosomes (Duval., *et al*. 2014). Skin pigments like melanin are produced and stored in melanosomes, which are intracellular, lysosome-like organelles. Skin gets its color from these pigments, which are then transferred to nearby keratinocytes (Yamaguchi and Hearing, 2009). The precursor to melanin production, the amino acid L-tyrosine, creates melanin via Figure 1 depicts a variety of spontaneous enzymatic processes, commonly referred to as the Raper-Mason route. Black-brown eumelanin and/or yellow-red pheomelanin are produced by the melanogenesis pathway, which takes place inside a melanosome. L-dopachrome raises tyrosinase activity, while L-tyrosine stimulates the development of melanosomes. Accordingly, maintaining the homeostasis of melanogenic systems depends heavily on controlling the amounts of L-tyrosine and L-DOPA (Yamaguchi and Hearing, 2009).

Tyrosinase is a 60–70 kDa glycoprotein that includes copper. It is thought to be a possible target for a number of therapeutic drugs because it is the enzyme that limits the rate at which the melanin production pathway proceeds. The microphthalmia transcription factor (MITF), a master transcription factor, controls the tyrosinase, TYRP-1, and TYRP-2 enzymes involved in melanogenesis. The adrenocorticotropic hormone (ACTH) and α-melanocyte-stimulating hormone (α-MSH), which are found in the dermis and epidermis, are important modulators of the melanogenesis pathway.

The various pigmentation disorders can have different histopathologies for hyperpigmentation. Retinal ridge flattening and epidermal thinning are two histological characteristics of melasma. elevated levels of melanin in the dermis and epidermis, as well as moderate perivascular Here, a lymphohistiocytic infiltration is seen. A greater number of dermal melanophages, their melanin deposition, and bigger melanocytes with noticeable dendrites are all suggested by immunohistochemistry analysis. Studies using electron microscopy revealed that melanocytes and keratinocytes have more melanosomes. The lymphocytes surrounding blood vessels in the dermal papilla and dermal melanophages exhibit elevated epidermal melanin content in PIH. Increased expression of several markers, including [CD]-68, c-kit, and MMP-2, can also be associated with peri-vascular lymphocytic infiltration, peri-follicular, and dermal fibrosis, highlighting the involvement of inflammation in the skin. There are two distinct histopathological types of PIH: dermal and epidermal.

While the latter is marked by increased pigment deposition in the dermis despite increased melano-genic activity in the epidermis, the former is characterized by increased melanogenesiand melanin deposition in the epidermis (Nicolaidou and Katsambas, 2014; Kang., *et al*. 2002; Silpa-Archa., *et al*. 2017; Isedeh., *et al*. 2016).

Current treatment for hyperpigmentation

As shown in Figure 2, the depigmenting and hyperpigmentation control agents may target different cell receptor antagonists, tyrosinase enzyme inhibitors, inhibitors of melanocyte stimulation, inhibitors of melanosome transfer, and degraders of formed melanin in keratinocytes. The most significant rate-limiting enzyme of the melanogenesis pathway, tyrosinase, is inhibited as part of the broadly targeted strategy.

Topical treatment

Site-specific skin hyperpigmentation is commonly treated or managed with topical medications, which have been developed

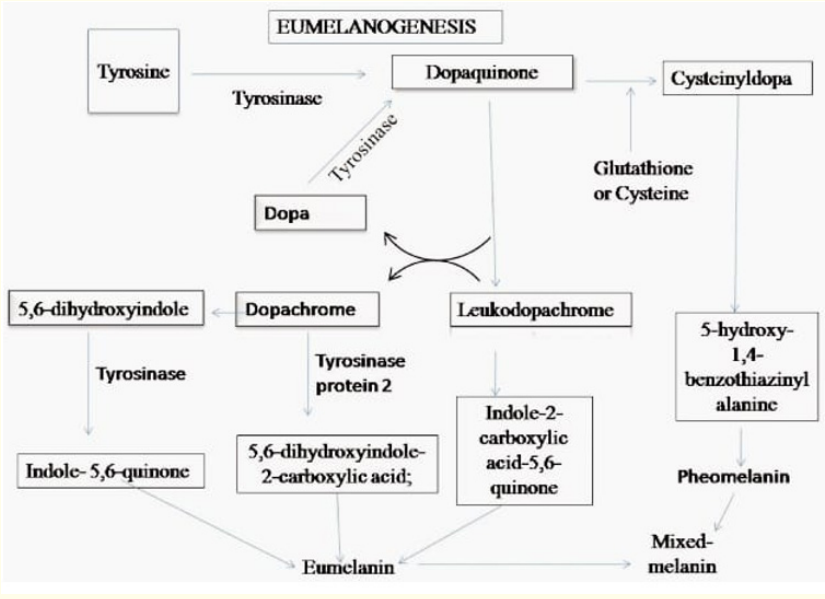

Figure 2

into topical dose forms including gels and creams. Since the 1960s, hydroquinone, the gold standard for treating hyperpigmentation, has been applied topically. It works by blocking tyrosinase, which prevents melanin formation. According to Haddad., *et al*. (2003), the products that are available have strengths up to 4%. Arbutin is a different substance that is derived from hydroquinone but has far fewer melanotoxic effects. Tyrosinase and melanosome maturation inhibition are the two mechanisms behind its depigmenting action. Arbutin's anti-tyrosinase action varies with dosage; nevertheless, greater dosages should be used with caution since they may result in paradoxical hypopigmentation (Piamphongsant, 1998).

Sugarcane is the source of the white, crystalline alpha hydroxy acid known as glycolic acid (Van Scott., *et al*. 1996). Glycolic acid has a concentration-dependent action. At lower doses, it causes keratinocytes to desquamate, while at larger quantities, it causes epidermolysis (Fischer., *et al*. 2010). Tyrosinase inhibition is one of the several mechanisms by which kojic acid is frequently utilized to treat hyperpigmentation issues. It primarily works by preventing tyrosinase's catecholase activity. According to a different study, kojic acid in keratinocytes forms the interleukin-6 protein, which has a depigmenting and anti-melanogenesis impact (Cabanes., *et al*. 1994; Choi., *et al*. 2012). Nonetheless, a number of clinical investigations have indicated that contact dermatitis is a frequent adverse reaction to kojic acid treatment (Nakagawa., *et al*. 1995).

Vitamin A, often known as retinol, and its structural and functional derivatives make up retinoid. Depigmentation is caused by a variety of mechanisms, such as impacts on inflammation, differentiation, and cell proliferation (Jacyk, 2001). Retinoids have no effect on the growth and shape of melanocytes, tyrosinase enzyme, or dopachrome tautomerase, but they do block the activation of the melanogenesis process by melanocyte-stimulating hormone (MSH) or L-tyrosine (Ebanks., *et al*. 2009). It has been proposed that retinoin, a first-generation retinoid and a naturally occurring derivative of retinol, might effectively prevent photoaging-induced hyperpigmentation (Bhawan, 1998; Weiss., *et al*. 1988). Retinoids' negative effects can be lessened by creating creams or gels with lower tretinoin concentrations (up to 1%) (Embiland Nacht, 1996). It has also been discovered that some third-generation synthetic retinoids, such as tazarotene (0.05 to 1%) and adapalene (0.1 to 0.3%), are safe and useful in the treatment of PIH (Grimes and Callender, 2006; Jacyk, 2001).

Tyrosinase is inhibited by azelaic acid, which also directly affects the melanogenesis pathway's ability to proliferate (Bergman and Luke, 2017). As with 4% hydroquinone, it has no effect on nor-

mal melanocytes and does not cause ochronosis with chronic use (Baliña and Graupe, 1991). The physiologically active analogue of vitamin B3, niacinamide, disrupts cell-signaling and prevents melanosomes from transferring to nearby keratinocytes. Route between keratinocytes and melanocytes, as indicated by a number of *in vitro* investigations. However, it has little effect on melanogenesis via suppressing tyrosinase activity or cell proliferation (Matts., *et al*. 2002).

Because the melanin synthesis pathway is a multi-step, intricate process, multiple topical agents can be used in tandem to act on distinct pathway steps, which suggests a rationale for topical agent combinations for synergistic effects or occasionally to lessen the unfavorable side effects of the other topical agent. As a result, numerous pharmaceutical companies have researched and even marketed a number of topical combinations. The most often utilized ingredient in mixtures with other substances like kojic acid, glycolic acid, azelaic acid, or corticosteroids is hydroquinone. Hydroquinone alone has not been demonstrated to be as therapeutically beneficial as these combinations (Ferreira Cestari., *et al*. 2007).

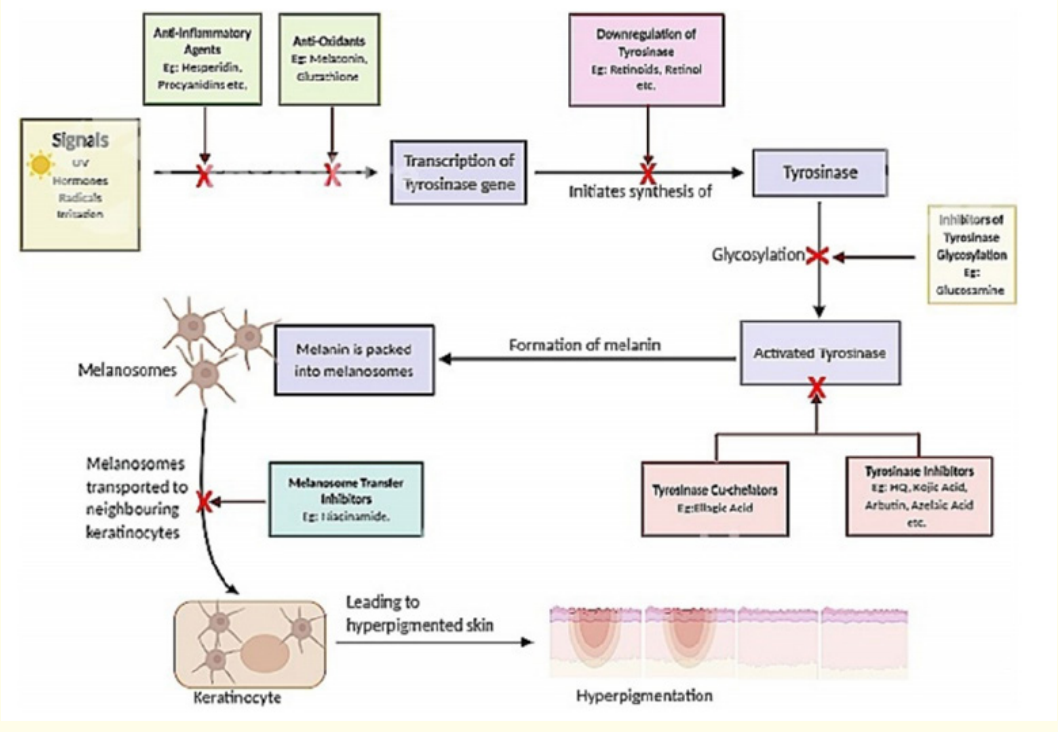

Figure 3

Oral treatment

Tranexamic acid is one of the oral medications that are thought to be a second-line treatment for hyperpigmentation. According to research on guinea pig skin, it lowers tyrosinase enzyme activity by blocking UV-induced plasmin activity, which lowers arachidonic acid and prostaglandins before influencing tyrosinase (Cho., *et al*. 2013; Kato., *et al*. 2011).

The pineal gland secretes the hormone melatonin, which has antioxidant and free radical scavenging qualities. It also inhibits the α-MSH receptor and activates several antioxidant enzymes, including glutathione peroxidase. A study found that topical melatonin by itself, in combination with 4% hydroquinone and oral melatonin, effectively reduced pigmentation in all individuals with melasma. Additionally, it reduced malondialdehyde levels and raised glutathione levels, indicating a reduction in oxidative stress (Hamadi, 2009). The body naturally produces cysteamine hydrochloride as a byproduct of the breakdown of the amino acid L-cysteine. Because of its ability to scavenge hydroxy radicals, 5% cysteamine considerably improved pigmentation in melasma patients compared to pla-

cebo, according to a randomized, double-blind research (Besouw., *et al*. 2013). The body produces glutathione, a tripeptide that has potent antioxidant properties. Through a number of mechanisms, including the suppression of the tyrosinase enzyme and the capacity to convert the synthesis of eumelanin to pheomelanin, it possesses skin-lightening properties (Sonthalia., *et al*. 2016). Ninety percent of participants in a clinical research said that a 50 mg glutathione lozenge moderately lightened or reduced hyperpigmentation (Handog., *et al*. 2016).Both topical and oral glutathione dramatically decreased the melanin index in melasma patients, according to another randomized, double-blind clinical research (Hashizume and Chan, 2014).

Because they can provide comparable therapeutic and histological results to topical Tretinoin, but in a shorter time frame of 2.5 weeks rather than 4-6 months, Tretinoin peels have been investigated (Cucé., *et al*. 2001). According to a study, the duration for skin contact was reduced from 4 to 8 hours to just 1 hour while keeping the same level of efficacy by raising the concentration of retinoin peel from 1% to 10% (Ghersetich., *et al*. 2010). Likewise, it has been discovered that glycolic acid peels help with hyperpigmentation conditions such post-inflammatory hyperpigmentation and melasma (Fischer., *et al*. 2010).

Laser therapy

One way to produce high-intensity monochromatic coherent light is through the use of stimulated emission of radiation, or lasers. The advent of laser therapy changed the available treatments for a number of skin conditions, particularly hyperpigmentation. Although there is ongoing debate regarding the safety and effectiveness of laser therapy, some hyperpigmentation conditions have seen positive outcomes.

The use of intense pulsed light (IPL) to treat hyperpigmentation has shown encouraging results. A xenon-chloride lamp that generates light with a broad spectrum is used in this process. It is commonly utilized for vascular lesions, melasma, hair removal, and melanocytic lesions because of the potential for changes in parameters including wavelength and fluence (Sarkar., *et al*. 2012). The Q-Switched Neodymium-doped Yttrium Alumi-num garnet (QS Nd:YAG) laser is another popular choice for hyperpigmentation. At low dosages, this laser is highly absorbed by melanin cells due to its longer wavelength and great selectivity, which prevents injury to the epidermis. Lee (2003).

By focusing on the vascular elements in lesions, pulsed-dye lasers, or PDLs, are thought to lessen melanocyte stimulation (Plonka., *et al*. 2009). Furthermore, although its process is similar to that of the QS Nd: YAG laser, the effectiveness of the Q-switched ruby laser, or QSRL, for hyperpigmentation has been extensively studied.

Types of hyperpigmentation

Melasma

- **Cause**: Hormonal changes that are frequently brought on by birth control pills, hormone replacement therapy, or pregnancy (sometimes known as the "mask of pregnancy"). Melasma gets worse in the sun**.**
- **Appearance:** Brown or grayish-brown spots that are typically found on the nose, upper lip, cheeks, and forehead**.**
- **Common Triggers: Heat**, Sun exposure, and hormonal shif.

Post-inflammatory hyperpigmentation

- **Cause:** Occurs following skin irritation or damage, such as burns, psoriasis, eczema, or acne.
- **Appearance:** Dark, flat patches on the skin where the inflammation or damage happened**.**
- **Common Triggers**: Infections, very harsh skincare procedures, or skin damage.

Sunspot

- **Cause**: Prolonged exposure to the sun, which causes UV-induced damage to accumulate over time.
- **Appearance:** On parts of the face, hands, shoulders, and arms that are exposed to the sun, there are tiny, flat, black blotches**.**
- **Common Triggers:** aging and UV radiation**.**

Freckles

- **Cause**: Exposure to sunlight and genetic predisposition.
- **Appearance:** Small, flat, light-to-dark brown patches that are typically found on people with fair complexion**.**
- **Common Triggers:** Melanin in areas prone to freckles is activated by sun exposure**.**

Age spots

- **Cause**: Sun radiation activates the melanin in freckle-prone areas.

- **Appearance**: Darker, larger areas that are typically seen in those over 40.
- **Common Triggers:** Age and UV exposure**.**

Drug-Induced Hyperpigmentation

- **Cause**: Some pharmaceuticals, including antibiotics, anti-malarial treatments, and chemotherapy drugs.
- **Appearance**: Darkening of the skin, usually brown or bluish-gray, in certain places or throughout the body.
- **Common Triggers:** Prolonged use of the drug.

Acanthsis

- **Cause**: Frequently connected to hormonal abnormalities, obesity, or insulin resistance.
- **Appearance**: Dark, velvety, thicker skin patches that are typically found in groin, armpit, or neck folds.
- **Common Triggers:** Diabetes, endocrine problems, and obesity**.**

Addisons disease-related hyperpigmentation

- **Cause**: Melanin production is elevated in a hormonal condition where the adrenal glands are not functioning properly.
- **Appearance**: darkening of scars, knuckles, gums, and sun-exposed areas.
- **Common Triggers:** Inadequate adrenal function.

Lichen planus pigmentosus

- **Cause**: Unknown, but skin damage brought on by the immune system might be involved.
- **Appearance**: brownish-black or ashy discoloration, usually on the neck, face, or flexural regions.

Ingredients table

S. No.	Ingredients	Role	Quantity
1.	Stearic Acid	Lubricant	2.5gm
2.	Coconut Oil	Moisturizer	3gm
3.	Glycerine	Surfactant	4gm
4.	Cetostearyl Alcohol	Opacifying agent	2gm
5.	Sodium benzoate	Preservative	0.1gm
6.	Phycocynine	Tyrosinase inhibitor	0.5gm

Table 1

Conclusion

Despite being the first-line treatment for hyperpigmentation, topical treatments can have negative side effects such skin irritation and peeling at higher dosages. The next second-line treatment is chemical peels, which have demonstrated good performance but are more costly and have a higher risk of side effects. Oral treatments typically have a higher recurrence rate and inconsistent outcomes. Third-line treatments include laser and microneedling [1-22].

Therapeutic alternatives because of the significant risks of adverse effects, the lack of data, and usage history. Furthermore, using sunscreens for sun and UV protection as a preventative or maintenance measure is still essential. Regretfully, current therapies have extended treatment periods and show little safety or effectiveness. As a result, a number of innovative formulations, promising treatments, and more recent therapeutic agents are being developed for the prompt management of hyperpigmentation with minimal side effects and short duration. However, researchers are currently working tirelessly on the clinical treatments of hyperpigmentation, and a guaranteed cure is still a pipe dream.

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