Title: Navigating Hyperpigmentation: Types, Pathophysiology, Treatment Approaches and Delivery Systems

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ABSTRACT

Hyperpigmentation, which mainly affects people with lighter skin tones due to elevated melanin levels, is a common skin condition. This condition frequently develops due to skin injuries like burns, acne, or rashes, resulting in various manifestations such as post-inflammatory hyperpigmentation (PIH), melanoma, telangiectasias, and epidermis. Melasma, appearing as brown patches predominantly on the face, is usually triggered by sun exposure and hormonal fluctuations, affecting mostly women. In contrast, PIH results from inflammation or injury causing localized darkening of the skin. While hyperpigmentation is largely harmless, it can significantly impact emotional well-being and self-esteem, particularly among middle-aged women and individuals with skin types III–VI. Treatment options prioritize both cosmetic and medical interventions. Topical agents, such as hydroquinone and retinoids, target the tyrosinase enzyme responsible for melanin production. Furthermore, chemical peels and laser treatments are employed for more severe cases, through they carry potential risks, including irritation and exacerbation of pigmentation. The process of melanogenesis is influenced by factors like hormonal changes, UV exposure, and inflammatory mediators. A multifaceted approach involving sun protection, targeted topical treatments, and occasionally procedural therapies is recommended for effective management. Additionally, novel drug delivery systems like liposomes and Transferosomes may enhance treatment efficacy. Understanding hyperpigmentation's causes and engaging in appropriate treatment can enhance skin health and foster self-confidence by achieving a more uniform complexion.

Keyword’s: Hyperpigmentation, Melasma, Post-Inflammatory Hyperpigmentation (PIH), Treatment, Melanogenesis, Delivery systems

1.INTRODUCTION

Due to a higher melanin concentration in darker skin tones, hyperpigmentation occurs frequently on skin of colour. Traumas that lead to damage, rashes, psoriasis, or bruises can

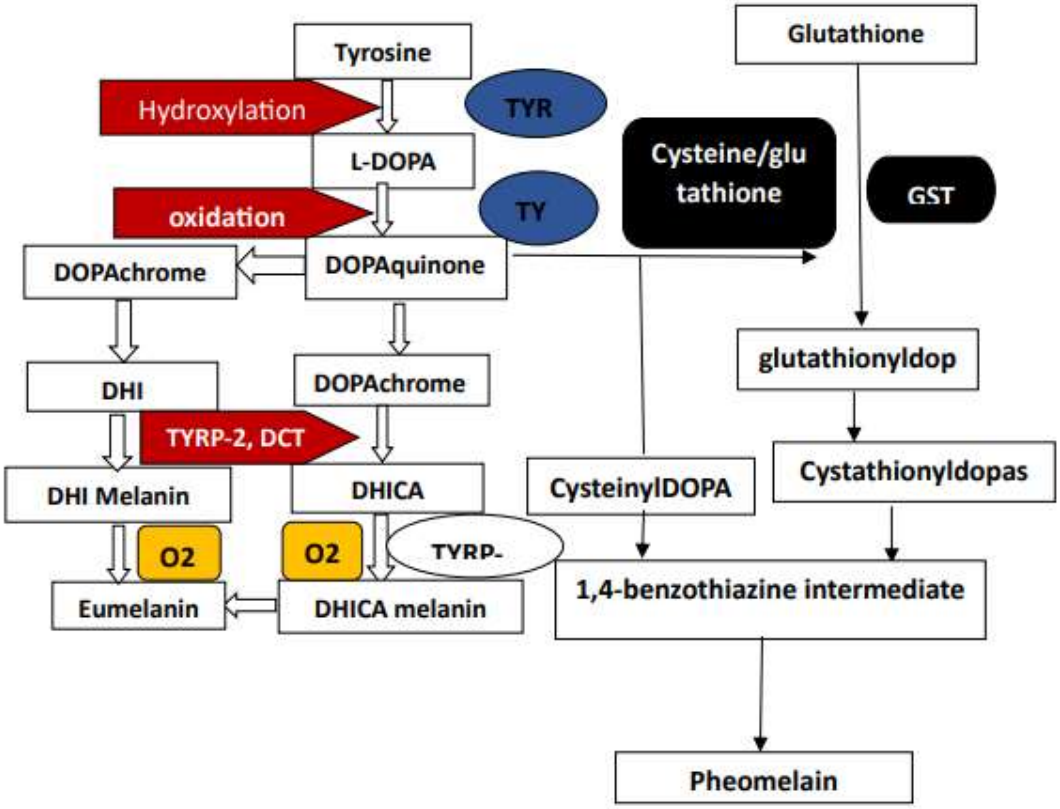
cause the skin to produce additional melanin, potentially resulting in dark spots[1]. Hyperpigmentation is a general term that encompassesa number pigmentations, darkening-related circumstances, and skin discolorations. Among the many hyperpigmentation disorders that are frequently observed are melasma, ephelides, lentigines, and post-inflammatory hyperpigmentation. The exposed areas of the skin exhibit uneven patches of light-to-dark-brown or gray-brown lesions, which are signs of Melasma, a skin condition caused by acquired hypermelanosis. It initially affects ladies and chiefly affects the expression and neck areasAnother hyper melanosis skin disease known as post-inflammatory hyperpigmentation (PIH) occurs when dark spots appear on the skin after an injury or inflammation. Known as "Age spots" or "Sunspots," solar lentigines is a disorder where areas of darker retinal lesions induce hyperpigmentation. Ephelides, often known as freckles, is another common condition that causes darker, pale brown to reddish spots to appear in one's face, neck, or arms. They form in childhood and are more prevalent in people with lighter or more fair skin tones. While discoloration is a common cosmetic concern among individuals of all skin types, it is particularly common in middle-aged women and persons with skin types III–VI. Hyperpigmentation can impair a patient's mental and emotional health, which can reduce their quality of life even if it is not considered a hazardous or fatal condition. For hyperpigmentation, there are numerous therapy choices. These substances are usually administered topically as ointments, gels, or creams. These topical medications can cause a number of adverse effects, including hypopigmentation, peeling, inflammation, and drying out of the skin. Prolonged treatment periods, which can last anywhere from a few months to years, may cause low patient satisfaction and compliance [2,3,4].

Why skin hyperpigmentation

Skin gets its colour from a chemical called melanin. Skin cells called melanocytes are in charge of making it. There are numerous circumstances or elements that might change the synthesis of melanin throughout your body. certain drugs can result in hyperpigmentation. Some women have changes in melanin synthesis and hormone levels during pregnancy. Hyperpigmentation can be caused by the uncommon endocrine condition Addison's disease. It is particularly noticeable that in exposure to the sun, like the hands, face, neck, and other places that come in contact with friction like the knees and elbows. It directly leads to hyperpigmentation of your body producing more of a particular hormone, which causes your body to produce more melanin [5,6].

2.PATHOPHYSIOLOGY OF HYPERPIGMENTATION

Neural crest cells are used in the embryonic production of melanocytes, which give skin its tegument colour. Near the junction of the dermal and epidermal layers, these basal layer cells generate melanosomes. Melanosomes produce and store skin pigments such melanin over an extended period of time, which are intracellular organelles that resemble lysosomes. The distribution of these pigments to neighbouring keratinocytes determines the color of the skin. Beginning with the amino acid L-tyrosine, followed by the production of melanin inside a melanosome, which results in the production of either yellow-red pheomelanin or black-brown eumelanin. Thus, maintaining the equilibrium of melanogenic systems requires regulating the amounts of L-tyrosine and L-DOPA [7,8].



Synthesis of Melanin

Being the rate-limiting enzyme in the route leading to the production of melanin and containing copper, tyrosinase, a 60–70 kDa glycoprotein, is considered a potential target for a variety of medical treatments. Microphthalmia transcription factor-MITF is the master transcription factor that controls the melanogenesis-related enzymes TYRP-1, TYRP-2, and tyrosinase. The two hormones that primarily regulate the melanogenesis pathway are adrenocorticotropic hormone, also known as AC and α-melanocyte-stimulating hormones (α-MSH), which are found in the epidermis and dermis.

As keratinocytes develop, melanosomes undergo various forms of degradation depending on the skin type. Melanin dust is formed by them in fairer skin types and darker skin. Numerous hyperpigmentation diseases can arise from disruptions in the normal process of melanogenesis caused by various external or intrinsic causes. UV, cAMP, and IL1 are examples of signals and factors that can increase and control Alpha-MSH is derived from pro-opiomelanocortin (POMC) peptides [9,10]. Melanosomes are transferred to nearby keratinocytes and the higher epidermis for DNA photoprotection upon UV exposure. In order to stop cell proliferation with unrepaired DNA damage, it triggers the death of keratinocytes in the upper epidermis that contain melanin. Additionally, keratinocytes secrete a number of Alpha-MSH and endothelin-1 (ET-1) are growth factors that contribute to UV induced hyperpigmentation [11,8]. Numerous intrinsic factors, such as signals from keratinocytes, endothelium cells, fibroblasts, inflammation-causing cells, hormones, and the neurological system, are involved in hyperpigmentation. ET-1 and NO (nitric oxide) may be released by these cells, which enhance melanogenesis [8]. Arachidonate-related chemical mediators that are known to stimulate tyrosinase activity, such as PGs (PGE2, PGF2a), Inflammation increases the release of thromboxanes and leukotrienes (LTC4, LTD4). Furthermore, it has been discovered that

muscarinic, alpha, and beta estrogen receptors are involved in the synthesis of cAMP and adenyl cyclase. The rise in estrogen levels associated with pregnancy may thus play a role in the emergence of hyperpigmentation conditions such as melasma and areolar hyperpigmentation [11]. With the different pigmentation disorders, hyperpigmentation can have different histopathologies. Melasma is marked by histological features like the flattening of the retained ridge and thinning of the epidermis. This area has a modest perivascular lymph histiocytic infiltration along with elevated melain levels content in the skin's outer layer and dermis. An elevated quantity of dermal melanophages and associated melanin deposition, along with bigger melanocytes with noticeable dendrites, are suggested by immunohistochemistry analysis. Studies using electron microscopy revealed that keratinocytes and melanocytes have more melanosomes. The lymphocytes in the dermal papilla and dermal melanophages surrounding blood vessels exhibit elevated epidermal melanin concentration in patients with peripheral ischemic hemolysis (PIH). In addition, Increased expression of several markers, such as [CD]-68, c-kit, and MMP-2, is linked to perivascular lymphocyte penetration, perifollicular, and dermal fibrosis, highlighting the significance of skin inflammation. For PIH, there are two different histological patterns: dermal and epidermal. While the latter is characterized by increased pigment precipitation in the dermis despite increased melanogenic activity across the epidermis, the former is differentiated by stronger melanogenesis and pigment deposition in the epidermis [12,13,14,15].

3.Types of skin hyperpigmentation

Melasma

Asymmetrical, uneven, brown-colored, reticulated macules on sun-exposed skin, particularly the face, are the hallmark of acquired hypermelanosis, also known as melasma. Melasma has been linked to genetic predisposition, prolonged UV exposure, and activation of female hormones [16]. Furthermore, it should be mentioned that melanogenesis, which is mediated through protein kinase by H_2 receptors has been demonstrated to be promoted by mast cell histamine release in response to UV exposure [17].

Melasma and Hormonal Effects

Given that melasma is commonly linked to pregnancy, hormonal contraceptive use, oestrogen therapy for prostate cancer patients, and conjugated after menopause, women's oestrogen, hormones play a part in the illness's development. Specifically, Progesterone and estrogen influence the melasma development. More people have melasma in compared to men in women. Unwanted effects on the skin of among the oral contraceptives is melasma. The melasma is commonly believed to be a hormonally caused skin alterations on a physiological level. The effects of estrogens substantial effect on pathological and physiological skin conditions, including as pigmentation. The many Progesterone and estrogen receptors regulate their biological processes [17,18].

4.Treatment / Management

4.1 Sunscreen

Visible light (VL) spans 400–780 nm, ultraviolet covers 290–400 nm, and infrared ranges from 8000 to 5000 nm. These three segments represent the primary divisions of the spectral range spectrum of solar radiation [19]. It is well known that UV and visible light exposure results in pigmentary changes, which are explained by a natural process where the skin produces reactive oxygen types (ROS), which triggers the production of inflammatory cytokines, and matrix-

degrading enzymes. A recent study also found that VL activates a calcium-dependent transcription factor linked to microphthalmia that is controlled by opsin 3 to cause persistent hyperpigmentation [20]. In light of this discovery, photoprotection against UV is crucial for melasma sufferers. In actuality, sixty-eight melasma patients were randomly assigned to one of two groups by Castanedo-Cazares et al. to obtain sunscreen that is UV-VL or UV-only [19]. After eight weeks, the former group outperformed the latter in terms of melanin assessment, colorimetric values, and scores associated with the (MASI), improving by 15%, 28%, and 4%, respectively [21]. A second RCT was designed similarly, comparing two groups of sunscreens that differed in the existence or lack of iron oxide, a pigment that absorbs that blocks UV rays. The authors found that the MASI score of the iron oxide group was significantly lower at six months. Even though white turbidity is an undesirable cosmetic problem, sunscreen with Zinc oxide, titanium dioxide, or iron oxide that is big (>200 nm) is strongly advised given this converging line of data [22].

5.Topical therapies

5.1Lightening agents for the skin

Topical skin-lightening medications are the mainstay of care for people with melasma. These medications target tyrosinase, an enzyme that restricts the pace of the melanogenesis pathway [23]. For many years, hydroquinone, one of the tyrosinase inhibitors, was the recommended treatment for hyperpigmentation. It is believed that hydroquinone prevents the enzyme's tyrosinase from either binding to it or engaging with the metal molecule at the enzyme's active site. This causes the melanosomes to produce less frequently, to change significantly in their internal structure, to degrade more frequently, and eventually to destroy the membrane organelles in the melanocytes [24]

5.2Hydroquinone

The main drug used to treat melasma has been hydroquinone, a hydroxy phenolic molecule, for a considerable amount of time. Because it may bind to copper and prevent tyrosinase from converting DOPA into melanin, it is effective at blocking this process [25]. Furthermore, hydroquinone has been shown to be involved in the degradation of melanocytes and melanosomes [26]. The study's findings showed that a cream with 4% hydroquinone, 0.05% a chemical called and 0.01% acetonide of fluocinolone was marginally more effective than 4% hydroquinone administered by itself or in conjunction with another ingredient [25,27,28,29]. The most commonly reported side result is irritating contact dermatitis, which manifests as burning, scaling, pruritus, and erythema to begin with. Up to 70% of patients have had this typical short-term adverse retaliation, and is mainly linked to Doses of 4% or more of hydroquinone, though it can occur at different hydroquinone concentrations [30,31]. In 2006, the Food and Drug Administration advised against using 1%–2% OTC hydroquinone doses. This was primarily brought on by reports of high absorption rates, exogenous ochronosis instances in human research, and possible carcinogenicity in animal investigations. With the passing of the CARES Act in 2020, this prohibition came into effect formally. At the moment, the only ways to obtain hydroquinone products are through new drug applications that have been authorized by the FDA or in patient-specific formulations. This change in regulation resulted from documented cases of exogenous ochronosis, even at low hydroquinone concentrations (1-2%), which were exacerbated by the widespread availability of uncontrolled over-the-counter hydroquinone [32,33,34].

5.3Topical retinoids

It has been demonstrated that topical retinoids are useful in treating melasma. Retinoids may promote keratinocyte turnover, prevent melanosome transfer, and let other topical medications to penetrate the epidermis [35]. When 0.1% cream containing tretinoin was compared with the vehicle over a 40-week period, Griffiths et al. found that 68% of the vehicle category and just

5% of the treatment group showed improvement in color measurement and histological evaluation. Surprisingly, 88% of patients who received treatment had side effects including erythema and desquamation, and the therapy's complete results did not show up until 24 weeks [36,37]. Given the lengthier duration of treatment necessary to achieve clinical improvement given the discomfort of tretinoin may not be a good substitute for monotherapy [38]. Adapalene, a synthetic retinoid, has been used to treat melasma [39]. Research comparing the use of tretinoin 0.05% cream and adapalene 0.1% gel by Asian Indian patients with melasma was conducted. The authors discovered equal efficacy in both groups, as evidenced by the higher tolerance of 37% and 41% drops in MASI score in the tretinoin and adapalene treatment groups, respectively.

5.3Triple Combination Therapy

Treatment for melasma with triple combination cream (TCC), which contains topical steroids, retinoid, and hydroquinone is popular [40]. In a major, multicenter, randomized controlled study, it was shown to be more efficacious than any single one of the three active components. The dual-combination group met exclusively 47% of the target goals, while 77% of patients receiving TCC therapy reported full or complete recovery. According to Ferreira Cestari et al., it was more effective than 4% hydroquinone [41]. Lesions that were nearly equivalent to perilesional skin, or melasma clearing, were observed in 35% of TCC individuals as opposed to 5% of hydroquinone only subjects.With dosages exceeding 4% and treatment periods exceeding three months,topical steroids are used to reduce ochronotic and other ingredient-induced irritation [43]. Hydroquinone's content is limited to 4% by the combination formula due to its combined actions with other components, which may explain the lower incidence of ochronotic [44].

5.4Investigational therapeutic approaches

Many topical medications that target every stage of cutaneous hyperpigmentation have been offered because research endeavors have revealed the physiology processes that contribute to the development and course of melasma. MTF-siRNA lotion considerably lightened Asian people's normal skin and brown face hypermelanosis by blocking Tyrosinase and its route [45]. Since Melanogenesis may also be inhibited by topical proton pump inhibitors (PPIs), like omeprazole, they hold potential as a treatment for melasma. as omeprazole was applied topically to people who had been exposed to UV light [46]. Omeprazole is thought to reduce melanogenesis via increasing tyrosinase degradation and reducing ATP7A. In addition to this discovery, Clinical case studies of people who develop vitiligo and have a relapse after using oral PPIs prove that PPIs can either induce or exacerbate the condition [47]. An oral antithyroid drug called methimazole is frequently used to treat hyperthyroidism. Notably, topical methimazole administration causes depigmentation; hence, its therapeutic usage may be advantageous for that post-inflammatory hyperpigmentation (PIH) and melasma together. Melanin synthesis is believed to be inhibited by methimazole, a potent peroxidase inhibitor [48]. Given that 20 patients receiving 5% daily methimazole showed no discernible changes in their blood concentrations of thyroid-stimulating hormone, free thyroxine, or free triiodothyronine, its adverse effects on thyroid function may be ignored [49].

5.5Chemical Peeling

Because chemical peels give the skin exfoliating agents, they are commonly used to treat melasma, which stimulates skin regeneration and tissue remodelling. Three layers make up the remodelling process: the papillary dermis affects the epidermis through the superficial layer; the papillary dermis affects the medium layer; and the mid-reticular dermis is penetrated by the deep layer [50,51]. People with darker skin tones are more likely than those with lighter

complexion to develop post-inflammatory hyperpigmentation, which makes managing melasma more challenging [52]. Chemical peels are a popular melasma treatment because they remove surface lesions and encourage tissue regrowth [53].

5.6Plant Ferments and Active Natural Substances

Natural extracts from diverse sources such as bacteria, fungi,plants and marine life show promise as potential melasma treatments.These substances known for their skin-lightening properties,may offer a gentler approach compared to synthetic chemicals [54].Korean Red Ginseng(KRG) a plant-based skin-lightening agent,is well-tolerated and offers numerous benefits in treating melasma [55]. By blocking tyrosinase activity, marine extracts such as Endarachne binghamiae, Schizymenia dubyi, Ecklonia Cava (EC), and Sargassum Silquastrum (SS) can stop the production of melanin [56]. Kojic acid,a fungal metabolite,is commonly used in combination with other ingredients to treat melasma [57].Fermented plants have emerged as a popular natural approach to skin lightening. Fermented aloe vera in particular offers a safe and affordable option that may replace harsh chemical ingredients. These natural remedies provide a gentler and potentially more effective alternative for addressing hyperpigmentation concerns [58].

5.7Other Antioxidants

Antioxidants are necessary for the management of skin conditions such as dermatitis.Substances including phytic acid, zinc, polypodium leucotomos, the B_3 vitamin (niacin), vitamin C (ascorbic acid), the antioxidant vitamin E, or amino acids are promising therapies.Compared to conventional glycolic acid peels, amino acid peels—especially those containing carboxylated 4-acidic amino acids—are kinder and more tolerable [59]. Vitamin C has been demonstrated to be beneficial in the treatment of melasma when combined with Q-switched Nd:YAG laser therapy[60]. Niacinamide, a reliable and potent variant of vitamin B3, can be utilized on its own to address melasma, thereby removing the necessity for more severe treatments such as hydroquinone[61]. Combining vitamin C with Q-switched Nd:YAG light therapy has been shown to be effective in treating melasma [62].

6.Systemic Treatments

Before prescribing systemic medications for melasma,health are providers should educate both themselves and their patients about appropriate dosages, possible adverse effects and the appropriate safety measures.Melasma can be treated with a variety of systemic medications.When combined with hydroquinone cream,oral P.leuco Dmos can serve as an adjunct therapy,potentially enhancing treatment outcomes [63,64]. A randomly allocated, double-blind, placebo-controlled clinical trial suggests that oral polypodium leucotomos extract, when combined with topical hydroquinone and sunscreen, may be a safe and effective supplemental treatment for melasma [65]. Oral tranexamic acid resulted in is a melasma therapy that is growing in popularity because it is inexpensive and simple to provide.Recently, randomized controlled trials were meta-analyzed has demonstrated its remarkable safety and efficacy in adult melasma patients [66].

7.Microneedling

Percutaneous collagen induction therapy, another name for microneedling, is a minimally invasive technique that uses microscopic punctures in the skin made with fine needles.Techniques like stamping, rolling needles, or electric pen instruments can be used to do this [67,68].The application of microneedling could improve transdermal medication delivery [69].Furthermore,the in vitro studies have demonstrated that the micro-wounds

created by microneedling can stimulate the activation of genes involved in epidermal cell differentiation and tissue remodeling [70].According to recent studies,microneedling in conjunction with topical treatments is efficient way to treat melasma [71,72].Microneedling,when combined with Laser Q-switched Nd:YAG (QSNYL) and 4% hydroquinone cream, has demonstrated enhanced efficacy compared to standalone topical or laser therapies [73,74,75].Potential side effects of microneedling include pain, swelling, bruising and temporary redness or burning sensations [76,77].

8.Lasers and Light-Based Therapy

Overview

Laser technology pioneered by Anderson and Parrish in the 1980's as revolutionized the field of dermatology.Their groundbreaking research emphasized how pigmented skin tissues have special thermal and absorptive qualities making them ideal targets for precise laser treatment.This innovative approach allowed for the selective destruction of targeted lesions,such as unwanted hair, tattoos and pigmented lesions while sparing surrounding healthy tissue [78]. Since it was first developed, laser therapy has broadened its uses to tackle various dermatological and cosmetic issues. These comprise pigmented lesions, lentigines, telangiectasias, hypertrichosis, vascular birthmarks, melasma, café-au-lait macules, solar lentigines, and tattoo removal [79].For patients with melasma who have not achieved satisfactory results with topical creams or chemical peels,laser therapy offers a promising alternative.By targeting the underlying mechanisms of melasma,such as increased melanin production and inflammation,laser treatments can help to reduce pigmentation and improve skin tone.

8.1 Intense Pulsed Lighting (IPL)

Devices that use extreme pulsed lighting (IPL) emit energy with wavelengths ranging from 515 to 1200 nanometers (nm). Within this range, melanosomes particularly absorb certain wavelengths of light.The fact that IPL technology has many wavelengths that enable simultaneous an additional benefit is the ability to target distinct stages of epidermal and epidermal melasma [80].Common adverse reactions that disappear in a day or two include mild erythema, or inflammation of the skin, and a slight tingling sensation.. A few patients may experience moderate skin exfoliation as a result of using greater energy levels; however, this usually recovers in about a week without leaving any scars [81,82].

8.2Q-Switched Low-Fluence 1064 Angstroms Nd: YAG

Q-switched lasers are frequently used to create areas of high intensity radiation with extraordinarily short pulse lengths. Their cardiac rhythm is almost a million times quicker than an IPL pulse. With a range of wavelengths, such as 533 nm or 1064 nm silicon aluminum zircon (Nd: YAG) laced with the metal, alexandrite gemstone (755 nm), and rubies (694 nm), these lasers are especially made to target melanin [83]. A Q-switched titanium anodised garnet (QSNY) laser doped with neodymium, which has a wavelength of 1064 nm, is a commonly used therapy approach for melasma patients Importantly, When using high-fluence QSNYL for melasma, post-inflammatory hyperpigmentation is a potential problem[84,85]. A new technique for using Q-switched lasers that is becoming more and more common is low-fluence or subthermolytic Q-switched treatment [79,86]. Because it penetrates the dermis more deeply and preserves more of the epidermis, 1064 nm is the wavelength most frequently used in low-fluence treatments. Sub thermolytic low fluences are used to treat melasma patients because it is believed. The pigment is broken down by the photoacoustic process that disrupts pigment while protecting the keratinocytes and melanocytes. Sub thermolytic Q-switched treatment

usually entails some degree of damage, but it is said to be less than that seen with conventional photo thermolytic methods [87]. When this technique is used in conjunction with other treatments, such as external biological (HQ), azelaic acid, peel with chemicals as Jessner's system that use glycolic acid (GA procedure), and systemic therapy, the greatest results and the lowest probability of recurrence are achieved [88]. Furthermore, recorded clinical trials have employed various laser typessuch as Er:YAG (2940 nm) laser, pulsed dye lasers (PDL), and no ablation 1550 nm erbium-doped fractionated photothermlysis. According to a comprehensive evaluation by CHEN et al., the laser combination treatment approach produces better outcomes than monotherapy. Combination therapy heals melasma through many channels, with their effects superimposed in a synergistic manner, which explains this. [89]. Even with the positive therapeutic outcomes, there is still a significant chance of recurrence after these operations, which renders this kind of treatment insufficiently successful. Early results with low fluence Q-switched laser therapy are promising, especially when using Nd: YAG lasers. But it requires several treatments over a short period of time (usually once a week) and has a very high 3-month recurrence rate, which can range from 64% to 81%. Patients' compliance to their treatment may be affected, and more sessions are typically required then for other bright and laser-based therapeutic approaches [90,91,92]. According to research on the treatment's LQSNY safety, side effects include erythema, transient burning, moderate edema, microcrust, hyper- and a lack of pigment, and telangiectasia. Notably, cases involving the combination of intense pulsed light (IPL), hydroquinone, glycolic acid, or microneedling with LQSNY have been found to have guttate hypopigmentation, with 5.5% to 13.6% incidence rates available [81,93].

8.3Non-Ablative Fractionated Resurfacing laser (NAFL)

Infrared light with a short wavelength uses four laser wavelengths1450, 1540, 1550, and 1927 nanometers. A non-ablative fractionated laser's mode of action is photothermolysis. Laser energy produces specialized thermal harm in the shape of microbeams with a diameter of over 400 μm and a depth of as much as 1000 μm when it passes toward or absorbed by tissues containing the water. Collagen fibres and keratinocytes are impacted by the development of tiny thermal zones (MTZ) brought about by this mechanism. Microscopic epidermal necrotic debris (MEND) are columnar keratinocyte necroses that form in the epidermis. This creation facilitates the migration of keratinocytes and dermal constituents into the stratum corneum, hence eliminating coagulated substances [94,95]. Melanin is detected in MENDs within six days of NAFLs being applied to melasma lesions. After a single NAFL treatment, enlarged melanocytes—which are frequently seen in melasma lesions—continue to decrease in quantity for up to three months. According to these findings, MENDs serve as "melanin shuttles," helping to remove melanin from the epidermis and dermis [96,97]. When NAFLs are utilized instead of IPL or Q-switched laser treatments, the clinical response seems to last longer. This is particularly crucial for patients receiving external tyrosinase inhibitors both before and after laser surgery [88]. In the majority of clinical studies, post-inflammatory hyperpigmentation (PIH) is a recognized adverse effect. The quantity among these microthermal zones appears to be associated with the appearance of PIH, which may occur from the heat produced during therapy. While recurrence can happen as soon as twelve weeks after IPL or Q-switched laser therapy is discontinued, NAFL treatments are linked to a greater risk of relapses in which are frequently observed between three and six weeks after treatment [79].

8.4Ablative Fractionated Resurfacing Lasers (AFL)

Studies have own that patients with melasma can benefit from fractional resurfacing lasers [98]. The light energy used by these lasers, such as Er:YAG (2,940 nm) as CO2 (10,600 nm), is

absorbed by the tissue's water molecules, causing tissue ablation [99].Micro-injury zones produced by fractionated ablation promote transdermal drug delivery (TDD), increase dermal elastin,remove melanin from the epidermis,stimulate collagen production,and stabilize the basement membrane.These effects reduce the interaction between melanocytes and keratinocytes,which lessens the appearance of pigmentation [93].The fractional approach also minimizes epidermal damage,lowering the possibility of adverse outcomes such dyspigmentation.In combination therapy,a CO2 laser with low fluency is often used as part of fractional ablative laser(AFL)treatments [100]. A recent prospective cohort study comparing the effectiveness of Jessner's solution peeling with and withoutAfter a single low-fluence fraction CO2 (10,600 nm) laser therapy session, there was no discernible difference in the two groups' improvements in mMASI scores. For melasma, both therapy modalities were determined to be secure and successful [101].

8.5Picosecond lasers

Innovative technology that can generate extremely brief pulses is represented by picosecond lasers. Unlike traditional photothermal methods,these lasers induce melanin fragmentation through extremely short pulse durations, reducing the amount of heat injury to the tissues around.Light from these lasers is emitted at a variety of wavelengths, most frequently 532 nm (KTP), 755 nm (alexandrite), or 1064 nm (Nd:YAG), which makes them extremely efficient in eliminating pigment[88,102].While promising, treatment of melasma using picosecond lasers is still relatively new.While some studies have suggested to ir efficacy,others have reported high recurrence rates, To evaluate the effectiveness of this new technique, more research is required[97,103].

9.Post Inflammatory Hyperpigmentation

A common acquired pigmentation disorder that develops after skin inflammation or damage is post-inflammatory hyperpigmentation (PIH). Individuals with darker skin tones (typing III–VI Fitzpatrick) are more likely to have it and to have it more severely and can be chronic. While it often resolves spontaneously over time, long-term treatment may be required. Combination therapy is generally considered the optimal treatment approach [104,105,106].

9.1Pathophysiology

Following inflammation,excessive melanin production or deposition occurs in the epidermis or dermis.This abnormal process known as post-inflammatory hyperpigmentation or hypermelanosis is triggered by inflammatory mediators. The epidermis produces more melanin as a result of these mediators' stimulation of melanocyte hypertrophy and activity. Large volumes of melanin are released into the dermis by damaged basal keratinocytes in deeper processes. The skin takes on a blue-gray hue due to phagocytosed and deposited melanin which may be persistent.Epidermal hyperpigmentation has a higher likelihood of resolving compared to dermal hyperpigmentation [104,107].

10.Treatment/Management

Management of post-inflammatory hyperpigmentation (PIH)typically involves a multi-faceted approach.The initial step is to address any underlying inflammatory condition.Subsequently,topical lightening agents,often in combination,can be employed to reduce hyperpigmentation.In more severe or resistant cases,chemical peels or laser therapy may

be considered. Additionally consistent daily sun protection is essential to prevent furtherdarkening and to promote overall skin health.

10.1Topical Interventions

Targeting Melanin Production: The Role of Tyrosinase Inhibitors

Hydroquinone remains a cornerstone treatment for melasma, but it can cause skin irritation. For those seeking a gentler alternative, mequinol can be considered.To enhance efficacy, these topical agents are often combined with retinoids or corticosteroids.A common triple combination includes hydroquinone,tretinoin,and fluocinolone acetonide.While the corticosteroid can mitigate irritation,it should be used judiciously to minimize the possibility of adverse effects. Retinoids like tretinoin, adapalene or tazarotene can be beneficial in treating underlying acne and PIH.Azelaic acid is another effective option for managing both conditions.

10.2.Chemical Peels

Chemical peels offer a popular approach to reduce hyperpigmentation by removing the epidermis' outermost layer. Even though these treatments work, they may cause skin irritation and make hyperpigmentation worse, especially in people with darker skin tones. To ensure optimal results and minimize risks, A competent dermatologist should be consulted in order to choose the optimum peel for your specific skin type and problems. Common types a chemical peels include those containing trichloroacetic acid, salicylic acid,and glycolic acid.

10.3Laser Therapy

Fractional photo thermolysis and laser therapies, Picosecond lasers, Q-switched ruby or Q-switched Nd:YAG have all been used to treat photo immunization, which target pigmented lesions and stimulating collagen production.However,as these treatments canpotentially irritate the skin and increase hyperpigmentation,they should be administered with caution by skilled professionals [101,108].

13.Novel Carrier systems used in management of Pigmentation

Novel carriers refer to advanced formulations designed to enhance the delivery and effectiveness of therapeutic agents, particularly in drug delivery systems.

Table:1 Novel Carrier systems used in management of Pigmentation

Carrier System	Description	Essential aspects	Results	References
Nano/Micro emulsions	Two immiscible phases (aqueous and oil) stabilized by surfactants.	- Enhance solubility of hydrophilic/lipophilic drugs - Low skin irritation and epidermal preservation.	- Kojic monooleate in nanomulsion showed a 54.76% survival rate for 3T3 cells.	109

			- Azelaic acid and hyaluronic acid nanoemulsions demonstrated strong skin penetration and reduced tyrosinase activity.	
Solidlipid nanoparticles	Form an occlusive layer promoting drug penetration and hydration.	- Improved stability, bioavailability, and drug entrapment - Effective delivery of tyrosinase inhibitors.	- Hydroquinone solid lipid nanoparticle gel exhibited 46.5% epidermal deposition compared to only 15.1% from hydroquinone gel.	110
Liposomes/Nanosomes	Spherical vesicles with phospholipid and cholesterol bilayers for hydrophobic/hydrophilic drug delivery	- Efficient drug administration - Enhances penetration through the stratum corneum - Nanosomes have a monolayer structure.	| - Liposomal serum containing azelaic acid resulted in a 41.7% to 85% improvement in melasma severity.	111,112,113
Transferosomes	Vesicular systems with lipid bilayer and an internal aqueous compartment designed for improved skin penetration.	- Ultra-deformable - Can penetrate through narrow skin pores - Enhanced flexibility due to phospholipids and surfactants.	- Designed with edge activators for enhanced deformability, optimizing drug delivery.	114
Niosomes	Nonionic surfactant vesicles forming bilayer structures for drug delivery of both lipophilic and amphiphilic substances.	- More cost-effective and chemically stable than phospholipids - Can provide controlled drug release.	- Effective in improving oral bioavailability and skin penetration of poorly absorbed medications.	115

Ethosomes	Ethanol-rich lipid vesicles designed for enhanced drug penetration into the skin.	- Higher ethanol concentration (20-45%) than liposomes - Facilitates deep tissue distribution and systemic circulation - Higher fluidity in vesicular structure.	- Capture a range of molecules and use both transcellular and intercellular pathways for drug delivery. - Vesicle size modulation based on phospholipid and ethanol concentrations.	116

14. Novel Formulations to treat Pigmentation:

Novel carrier	Drugs	Reference
Solid lipid Nanoparticles	Kojic Acid Di palmitate, Hydroquinone, Azelaic acid	117
Nanoemulsion	Kojic Acid Dipalmitate, Azelaic acid	118
Ethosomes	Kojic Acid Dipalmitate, Kojic Acid, alpha arbutin, Azelaic acid	119
Liposome	Arbutin, Hydroquinone, Azelaic acid, Glabridin	120
Niosomes	Arbutin, Hydroquinone	121
Transferosomes	Azelaic acid	122

Table: 2 Novel Formulations to treat Pigmentation

Conclusion: People with darker complexions are more likely to suffer from hyperpigmentation, which is a range of skin conditions marked by an overabundance of melanin. Melasma, ephelides, and post-inflammatory hyperpigmentation are among the conditions that frequently result from exposure to UV light, hormone fluctuations, and skin damage. Although hyperpigmentation is mostly benign, it can significantly affect a person's sense of self and quality of life. Chemical peels, topical medications, and laser treatments are

among the various therapy methods. These treatments are intended to reduce melanin production and enhance the appearance of the skin; however, they may have adverse effects and need to be applied consistently to be effective. As research advances, customized treatment strategies are crucial for controlling hyperpigmentation disorders in order to maximize results and improve patient satisfaction. The cosmeceutical sector is expanding exponentially in response to the growing demand for cosmeceutical goods. The cutting-edge technologies of the twenty-first century are represented by nanotechnology, which promises remarkable prospects for research platforms and the marketplace. The unique properties of liposomes, Niosomes, transferosomes, and other similar materials have drawn particular attention because of their capacity for increased permeability and higher bioavailability. Thus, liposome-based cosmetics may be a blessing in the treatment of skin conditions

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