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DEMYSTIFYING HYPERPIGMENTATION: A JOURNEY FROM DARK TO LIGHT

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ABSTRACT

Hyperpigmentation is a disease of the skin where there is disruption of the production of melanin that causes skin disorders. The major work of melanin is to absorb the dangerous UV and convert it into heat energy and thus preventing skin disorders. Usually, it does occur in two forms, viz, hyperpigmentation disorders and Hypopigmentation disorders. There will be either an increase in melanin production or a decrease in it, resulting in certain types of disorders. Melasma, post-inflammatory hyperpigmentation, solar lentigines, vitiligo, etc., are some of the usual disorders of pigmentation. Hyperpigmentation of any kind creates a huge social and emotional impact on the person, specifically on the individuals whose pigmentation involves parts that are noticed, like the face, hands, feet, neck, and gum. Multiple remedies can be followed by the topical route, oral route, laser therapy and chemical peeling, and new kinds of remedies that have a better result to overcome pigmentation. They included hydroquinone derivatives such as azelaic acid, kojic acid. Even newer alternatives such as cysteamines, peptides, 4-n-butyl resorcinol, laser therapy, chemical peel, and new formulations are also gaining wide usage now, as there are fewer side effects of these newer formulations. Such medications suppress the activity of tyrosinase, and as a result, melanin cannot be produced. Such a review is more on the introductory overview of the hyperpigmentation, the causative

factors, types and the various approaches of treatment of pigmentation, as well as the importance of having new and emerging forms of treatment of pigmentation.[1,2]

KEYWORDS: Hyperpigmentation, melanocytes, tyrosinase, inflammation, combination treatment, pigmentation disorders, novel therapies.

INTRODUCTION

Hyperpigmentation merely means the darkening of the skin texture. It can be described as an indication of an intrinsic genetic, metabolic, or neoplastic disease. Melanocytes play the most critical role, and a great number of disorders can lead to increased melanin accumulation in the skin. Melanocytes are progenitor cells of a specific nature whose origin is a subset of multipotent stem cells in the neural crest. The precursor cells are known as melanoblasts, and the melanoblasts migrate to the basal epithelium layer of the flesh. They synthesize melanin in organelles that are lysosome-related (melanosomes). The most prevalent cases of hyperpigmentation disorders are Melasma and postinflammatory hyperpigmentation, which are common among millions of people across the world. Melasma tells us about hyperpigmented macules on the face; it is mostly expressed in people having skin types III, IV, and V in the Fitzpatrick skin scale and mostly in females. Transference factors in which melasma develops are genetic predisposition, hormonal factors, contraceptive agents associated with the condition, and too much exposure to the sun. Post-inflammatory hyperpigmentation is an acquired form of hypermelanosis that appears after any cutaneous injury or inflammation in the skin and is predominant on the colored dark individuals. Any skin injury, insect bites, allergic reactions, medication-induced hyperpigmentation, burns, cosmetic procedures, etc., are the main causes of PIH. Hyperpigmentation is not a harmful disease, but it affects the quality of life of the patients as it leads to their psychological health as they feel excluded by society. Treatment of hyperpigmentation can be done using various methods. Some are used topically i.e. as creams, gels, ointments, some are by mouth, either orally or intravenously. All treatments have their side effects, which include drying, irritation, peeling or hypopigmentation. The therapy takes months to years and leads to low patient compliance and satisfaction. The therapy requires time, tolerance, tolerability, and uniformity to bring out the optimum results possible. Various types of regions undergo hyperpigmentation, such as hyperpigmentation around the gums, neck region, elbows, knees, and face. Among these, the most common is facial hyperpigmentation, which affects patients completely by bringing insecurities in them. The goal of this article is to examine

hyperpigmentation completely with a special emphasis on novel treatment and their mechanism.[3,45,6]

2. Causes And Types of Hyperpigmentation

Hyperpigmentation causes are numerous; some of the problems that often bring them about are genetic, sun exposure and some medicines.

2.1: Genetics: The genetic constitution of an individual also determines the skin color. An individual controls the amount of melanin that they produce. Genetics has the capability of describing the number of melanocytes that are produced by a given person and thus have the ability of altering the skin color. Nearly 125 genes are found to have effects on skin tone in a person.

2.2: Sun Exposure: Sun exposure has been found to be another reason of hyperpigmentation. This is because the body produces more melanin in order to shield the skin against the UV rays thereby causing the skin to be pigmented.

2.3: Drugs: There are a number of drugs that could darken the skin or lighten it. As an example, the pigmentation may be increased by antibiotics and birth control pills, and therefore it is important to consult a doctor about pigmentation-related health results of medicines.

Types

There are various types of pigmentation; the classification is based on various factors.

Epidermal Melanosis

In this type of pigmentation, the skin shows only excessive amounts of melanin, but a normal number of melanocytes is found. For example, urticaria pigmentosa.

Dermal melanosis

In this type of hyperpigmentation, the epidermal melanin is normal; the pigmentation is caused by melanin within the dermis. For example, incontinent pigment. The colour of the lesion is brown and grey.

Mixed type

This type of hyperpigmentation is characterised by increased melanin in the epidermis and melanophages in the dermis. For example, post-inflammatory hyperpigmentation after any laser treatment or acne, etc.

Melasma

It is hypermelanosis of sun-exposed areas of the skin that is progressive and is predominantly located on the face. It can be idiopathic or caused by some medications, hormone imbalance, pregnancy, oral contraceptives, or anticonvulsants (phenytoin). It is predominant in skin types 4, 5, and 6. Melasma is spread across three areas of the face that is, centrocentrifugal (63 percent), malar (21 percent), and mandibular (16 percent).

Post-inflammatory Hyperpigmentation

Such a form of hyperpigmentation is caused by the effect of trauma, injury, and inflammation. It can be a result of laser treatment, light treatment. It causes a lesion to develop, and this can last for a few months to years.

Solar Lentigines

These can also be called liver spots. Such are macular lesions located on the skin parts exposed to sunlight. These can have a color range of light-yellow to dark-brown. Mostly, the chest, back, face, hands, forearms, and shins are attacked.

Vitiligo

The loss of melanocytes is the most common pigmentation disorder, termed as vitiligo, characterised by the development of chalky white macules that are scaly. It is predominant among black colored people. The pathophysiology of this illness is not known, and it is an autoimmune disorder. Cosmetic surgeries are employed in its treatment.[8,9,10]

Treatment for Hyperpigmentation

Depigmenting agents with multiplicity in use are in existence, and they constitute cell receptor antagonists, melanocyte inhibitors, tyrosinase enzyme inhibitors, and inhibitors of melanosome transfer. The most popular targeted treatment is the inhibition of tyrosinase. It can be topical treatment, oral treatment, chemical peels, laser treatment, or some new modes of treatment.

Topical Treatment

The most common topical care is preferred when dealing with hyperpigmentation. The dosage form includes creams and gels mainly.

The most popular agent applied in the treatment of hyperpigmentation therapies like melasma, after post-inflammatory hyperpigmentation, is topical hydroquinone. Its molecular form is C6H6O2. The mode of action of Hydroquinone is that it blocks the enzyme called tyrosinase that is active in melanin biosynthesis; melanin is the chemical that causes pigmentation of the skin. Many studies have demonstrated that hydroquinone is characterized by side effects running along the lines of skin irritation, ochronosis (thickening/grey-blue darkening of skin).[11]

RETINOIDS

Retinoid is a substance whose use is very common to treat hyperpigmentation; its active component is called Tretinoin (0.05- 0.1 percent). It acts by preventing the transcription of tyrosinase as well as breaking the synthesis process of melanin. It has a number of side effects, which are the increase in pigmentation, irritation, erythema, and peeling.

Azelaic Acid

The reversible inactivator of tyrosinase is Azelaic acid, which is available at a concentration of 15-20 percent and can cause cytotoxic and antiproliferative effects on melanocytes. A stronger effect on skin lightening is achieved by combining avobenzone and tretinoin. It presents many side effects, so as scaling, burning, and pruritus.

Kojic Acid

Kojic acid is a naturally occurring chemical that is of fungal origin. It is applied in the treatment of various hyperpigmentation diseases. It functions by suppressing the enzyme tyrosinase that plays the role of the manufacturing of melanin, thus lightening the spots and making the skin paler. It is in the form of soaps, serums, and creams.

Peptides

Pigmentation treatment became one of the new things in the form of peptides. These enhance the synthesis of collagen and inflammation. One popular Peptide is palmitoyl pentapeptide (Matrixyl). It is a collagen stimulator that makes skin more elastic, smooth, and firm. It is

implanted in the stratum corneum and penetrates the dermis; then it attaches to a receptor located on the cell surface. It enhances the production of collagen.

4-4-n-Butylresorcinol

It directly suppresses that of tyrosinase and TRP-1. It depicts fast action and high efficacy, and very good tolerability in the melasma patients. The outcome can be observed in 8 weeks. This is safer in comparison to Hydroquinone, which is known to cause cytotoxicity since 4-n-Butylresorcinol does not exhibit cytotoxicity but selectively inhibits melanogenesis. When combined with 4-n-Butylresorcinol, cysteamine has a more evident impact, i.e., it relieves several side effects and results in improved effectiveness.

Cysteamines

One of the new therapeutic modalities for long-term pigmentation disorders is cysteamine. It inhibits these enzymes, the tyrosinase and peroxidase, which play a very important role in the melanin biosynthesis pathway. It lowers the oxidant stress, which may lead to pigmentation since it exhibits antioxidant attributes.

Oral treatment

Applying drugs containing pigmentation is used, which is administered orally; it belongs to the second-line treatment. Most frequent one is Tranexamic acid whose mechanism is such that it reduces the activity of tyrosinase by inhibiting the activity of UV induced plasmin which further decreases the arachidonic acid as well as prostaglandins that would influence the activity of tyrosinase and helps in reducing the pigmentation Other than its action, it has several side effects too such as, abdominal pain, nausea, and vomiting, numbness, tinnitus, facial pruritus. There are others, such as glutathione, isotretinoin, which are also administered orally in the treatment of pigmentation.

Chemical peels

This form of pigmentation disorder treatment is popularly referred to as Chemical peeling or Chemoexfoliation. Compared to others, it is not so expensive, and well is less harmful. It is applied to cause an injury at the point of certain skin depth to stimulate the development of new skin with clear texture, appearance, and a better surface. It is typically applied to the problem of acne and damaged skin due to photodamage. These are the conventional choices, and usually glycolic acid at a concentration of 20 70 percent and salicylic acid of 20 30

percent. Some of the side effects of peeling are a tingling feeling, mild burning, sensitivity, and erythema.

Laser Therapy

Laser therapy of pigmentation carried a lot of importance as it was introduced. But the safety and efficacy of lasers is not so great; however, a good outcome is being seen in a large number of patients being treated by lasers. Different kind of therapies is administered in various wavelengths, depending on the level of pigmentation. These include hard Pulsed Light laser with the wavelength of 500-1200nm, pulsed Dye Laser with the wavelength of 585nm, and Q-Switched Ruby Laser with the wavelength of 694nm. However, laser therapy is not safe enough.[12,13]

Novel Therapy

To eradicate the negative consequences of the other therapies, numerous new formulations were invented as an alternative to manage hyperpigmentation. A few of the formulations are:

Solid lipid nanoparticles

Other solid nanoparticles are in use to treat hyperpigmentation, and these are topically applied because solid nanoparticle forms an occlusive layer of the skin and have increased drug penetration, piercing deep into the skin, having its superb effect. All these are more stable and bioavailable and play different tyrosinase inhibitors that are developed using lipid nanocarriers.

Liposomes/Nanosomes

Liposomes are microscopic model vesicles that take a spheroid shape, and their compositions consist of concentric bilayers of phospholipids and cholesterol. The liposomes have the potential to simply fuse with the cell membrane and modify the membrane and boost the penetration through the stratum corneum, and therefore, the drug is efficiently delivered. The combination of 4-n-butylresorcinol and Azelaic acid with retinol is used as a liposomal serum that has now been found to be better in treating melasma.

Microemulsions

Micro-emulsions have two immiscible phases, which are the aqueous phase and the oil phase. These are the vehicles that can be used in cosmeceuticals. They are utilized in the form of the topical administration of drugs because they are readily absorbed through the topical route

owing to their size and good solubility, e.g., microemulsion of hydroquinone. It is applied in the treatment of melasma.

CONCLUSION

Skin pigmentation refers to the colour of an individual's skin, and pigmentation is customary to the amount of melanin that is produced by the melanocytes of an individual's skin. When the skin colour is dark, it implies that more melanin is being produced by the body and is said to be hyperpigmentation, and when the amount of melanin produced by the melanocyte is small, then it will result in hypopigmentation. It is either genetic, hormonal, or caused by some medication. The two somehow hurt the individual, and therefore, what is required is a safer drug, one that has high tolerability and high efficacy. They use topical therapies such as hydroquinone and its derivatives, and all of them cause irritation as well as ochronosis. There are also oral treatment methods that are effective but demonstrate several adverse effects. This was followed by the introduction of laser therapy, which treats hyperpigmentation by application of different wavelength radiations of light in fighting off the pigmentation, but the demerit of the laser therapy is that it is not very safe. To counteract all these side effects of the existing treatments and to come up with a treatment that is highly tolerable, highly effective, and safe for administration, several new formulations were studied, and these comprised nanoparticles, microemulsions, phytochemicals, and were found to demonstrate positive responses with minimal side effects.

Future Perspectives

Quite a large number of medications have been found to clear the pigmentation disorders, but with lesser or more side effects, thus interfering with the treatment procedure. Conversely, the scientists ought to consider the herbal alternatives since these contain no side effects, and they are also effective. As it occurs even up to date, there are numerous herbal remedies used in the treatment of pigmentation disorders conditions though there are still some herbal plants that are yet to be characterised towards the treatment of pigmentation-related diseases.

REFERENCES

1. Speeckaert R, Van Gele M, Speeckaert MM, Lambert J, van Geel N. The biology of hyperpigmentation syndromes. Pigment Cell & Melanoma Research., 2014 Jul; 27(4): 512–24.
2. Schalka S. New data on hyperpigmentation disorders. Journal of the European Academy of Dermatology and Venereology, 2017 Sep; 31(Suppl 3): 18–21.

3. Taylor SC, Grimes PE, Lim J, Im S, Lui H. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. Journal of Cutaneous Medicine and Surgery, 2009 Jul; 13(4): 183–91.
4. Nautiyal A, Wairkar S. Management of hyperpigmentation: Current treatments and emerging therapies. Pigment Cell & Melanoma Research, 2021 Nov; 34(6): 1000–14.
5. Ko D, Wang RF, Ozog D, Lim HW, Mohammad TF. Disorders of hyperpigmentation. Part II. Review of management and treatment options. Journal of the American Academy of Dermatology, 2023 Feb; 88(2): 291–320.
6. Yoo J. Differential diagnosis and management of hyperpigmentation. Clinical and Experimental Dermatology, 2022 Feb; 47(2): 251–8.
7. Thawabteh AM, Jibreen A, Karaman D, Thawabteh A, Karaman R. Skin pigmentation types, causes and treatment—a review. Molecules, 2023 Jun 18; 28(12): 4839.
8. Nieuweboer-Krobotova L. Hyperpigmentation: types, diagnostics and targeted treatment options. Journal of the European Academy of Dermatology and Venereology. 2013 Jan; 27(Suppl 1): 2–4.
9. Plensdorf S, Martinez J. Common pigmentation disorders. American Family Physician, 2009 Jan 15; 79(2): 109–16.
10. Plensdorf S, Livieratos M, Dada N. Pigmentation disorders: diagnosis and management. American Family Physician, 2017 Dec 15; 96(12): 797–804.
11. Fabian IM, Sinnathamby ES, Flanagan CJ, et al. Topical Hydroquinone for Hyperpigmentation: A Narrative Review. Cureus, 2023 Nov 15; 15(11): e0.
12. Lynde CB, Kraft JN, Lynde CW. Topical treatments for melasma and postinflammatory hyperpigmentation. Skin Therapy Letter, 2006 Nov 1; 11(9): 1–6.
13. Jimbow K, Minamitsuji Y. Topical therapies for melasma and disorders of hyperpigmentation. Dermatologic Therapy, 2001 Jan; 14(1): 35–45.
14. Pai VV, Bhandari P, Shukla P. Topical peptides as cosmeceuticals. Indian Journal of Dermatology, Venereology and Leprology, 2017 Jan; 83(Suppl 1): 9.
15. Kolbe L, Mann T, Gerwat W, et al. 4-n-butylresorcinol, a highly effective tyrosinase inhibitor for the topical treatment of hyperpigmentation. Journal of the European Academy of Dermatology and Venereology, 2013 Jan; 27(Suppl 1): 19–23.