Since 1987
REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION |38 (Sup1): 7-12 (2024) Rcpp

Received: 18 December 2023 | **Accepted**: 22 December 2023 | **Published**: 17 February 2024

Paper presented at the **1st Conference of the Hellenic Scientific Society of Aesthetics**
2-3 December 2023 | University of West Attica, Athens, Greece

Open Access | **Review Paper**

Skin whitening as an aesthetic procedure for the treatment of facial dyschromia

Evangelos Adamtziliadis[1,*], Efstathios Rallis[1], Niki Tertipi[1], Eleni Sfyri[1], Eleni Andreou[1], Foteini Biskanaki[1], Vasiliki Kefala[1]

[1]Sector of Aesthetics and Cosmetology, Department of Biomedical Sciences, School of Health and Care Sciences, University of West Attica, Athens, Greece.

***Corresponding author**
Evangelos Adamtziliadis, BSc, University of West Attica, Agiou Spiridonos 28, Egaleo 122 43, Athens, Greece.
E-mail: vaadamtz@hotmail.com

Abstract
Facial dyschromia cause problems in the appearance, resulting in negative psychological and social effects that degrade the quality of life of a person. They are the result of excessive accumulation of melanin in various parts of the epidermis due to excessive melanogenesis, which is either caused by a reaction to the effect of ultraviolet radiation or, in most cases, has a pathological etiology. The present article presents the various methods of skin whitening that can be used through Aesthetic practice.

KEYWORDS
facial dyschromia, skin whitening, melanin, hyperpigmentation, whitening agents, chemical peels, IPL, dermabrasion, microneedling

How to cite: Adamtziliadis E., Rallis E., Tertipi N., Sfyri E., Andreou E., Biskanaki F., Kefala V. Skin whitening as an aesthetic procedure for the treatment of facial dyschromia. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38 (Sup1): 7-12 (2024). https://doi.org/10.61873/MHWV3039

Publisher note: PHARMAKON-Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. INTRODUCTION

Exposure to sunlight is related to harmful effects of UV radiation on the skin, such as the creation of reactive oxygen species (ROS) that lead to the oxidation of the skin, damaging its healthy cells, resulting in a general deterioration of quality, appearance and health of the skin tissue that appears in the form of pigmentary changes [1], photoaging, even precancerous lesions.

Facial dyschromia refers to color changes of the skin that cause inhomogeneity in pigmentation. They usually appear as hyperpigmentation (darker spots), leading to a color uneven appearance that deviates from the skin's normal color tone. They cause an appearance problem, with consequent negative psychological and social effects that degrade the person's quality of life [2,3]. Hyperpigmentation of the skin is usually caused by

excessive production, accumulation, distribution or transport of melanin [3,4].

The color of the skin is determined by the amount of pigments present in it and the ratio between them. The central pigments of the epidermis are derivatives of melanin. The two most important forms of melanin found in humans and whose ratio determines, mainly, the final color of the skin, are eumelanin, with a dark brown/black color and pheomelanin, with a yellow/red color [5-9]. The higher proportion of pheomelanin compared to eumelanin characterizes fair color skin types [9]. The main function of melanin is to protect the skin from the harmful effects of ultraviolet radiation [1,6,8-11,13,14].

Melanin production is induced after exposure to UV radiation [5,9-11] and occurs in specialized cells, the melanocytes, located at the border between the dermis and the epidermis, in the basal layer of the epidermis [1,5-8,11-16]. Each melanocyte is surrounded by approximately 36 keratinocytes [8,10,11,15]; these two form the epidermal melanin unit [10,13,15]. Melanin is transported to the neighboring keratinocytes of the epidermis [5,7,8,11] via dendrites [13,15].

Melanogenesis is the complex multifactorial process of melanin production. Melanin is synthesized by the oxidation of the amino acid L-tyrosine [6,9], and is stored in melanosomes within keratinocytes [1,16]. Melanosomes (microscopic cysts inside the melanocyte [17]) contain tyrosinase (TYR), a glycosylated polyphenol oxidase [13] which is a copper-containing enzyme. Melanin synthesis is mainly controlled by tyrosinase, which catalyzes two distinct reactions in melanin synthesis, namely the hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), by monophenolase action, and its oxidation (L-DOPA) to the corresponding quinone, L-dopaquinone (DQ), with biphenolase activity [17].

Pigmented lesions are often benign and easily distinguishable, accordingly to their appearance and location [3]; based on the location of the pigment, they can be classified into epidermal, dermal, and mixed (epidermal and dermal lesions) [2,4]. Another classification is their separation into congenital or acquired [2], while they can still be classified based on their etiology as nephrotic, post-inflammatory, hereditary or acquired drug-induced, hormonal, etc. [4]. The classification in these ways assists in the selection of the appropriate, case-by-case, treatment. In general, epidermal lesions are easier to eliminate than dermal lesions, due to their proximity to the surface of the skin. Dermal pigmentations rarely respond to treatment with local agents or aesthetic procedures, such as superficial peelings, while they are more effectively treated by lasers due to the precise selectivity and depth of penetration of the laser beam into the skin [2]. In general, the epidermal pigmentary lesions are linked to diseases such as ephelides, solar lentigo, café-au-lait macules, naevusspilus, etc. The dermal are linked to diseases such as blue naevus, Ota naevus, Ito naevus, Hori naevus etc. The mixed are linked to diseases such aspost-inflammatory hyperpigmentation, melasma, nevocyticnaevus, naevus Becker etc.

2. SKIN WHITENING METHODS USED IN THE AESTHETICS PRACTICE

Skin whitening is the best way to treat skin hyperpigmentations. It includes the various methods aimed at brightening the skin [8,12], resulting in a more uniform and improved complexion [8,13]. Skin whitening leads to skin discoloration achieved by reducing the concentration of melanin in the skin [12,13], inhibiting either the maturation of melanocytes or the process of melanogenesis, mainly by selectively suppressing the activity of tyrosinase (TYR) to reduce hyperpigmentation [12,15], by preventing the transfer of pigment granules (melanosomes) from melanocytes to surrounding keratinocytes [15], by suppressing pigment biosynthesis and through some alternative pathways [12].

Skin whitening methods used in the Aesthetics practice include the topically applied whitening agents, the chemical peels, the light emitting therapy treatments, the dermabrasion, the microneedling.

2.1. Topically applied whitening agents

Topical application of whitening agents to the skin is the first treatment option, mainly because this method is less invasive and aims to interfere with the process of melanogenesis and transfer of melanin to the keratinocytes, through various mechanisms, as an attempt to actually treat the problem. Whitening agents appear in various cosmetic forms, mainly creams, emulsions and lotions, intended to succeed in either the discoloration of already existing melanin in the skin or suspending the creation of new melanin.

Some of the mechanisms of action of the topical application of whitening agents (related to agents that affect them, indicatively) include:

a) tyrosinase inhibition (kojic acid, ellagic acid, resveratrol, oxyresveratrol [18], hydroquinone, mequinol, azelaic acid, arbutin [14,18], deoxyarbutin, licorice extract, N-acetylglu-

cosamine, glycolic acid, N-acetyl-4-S-cysteaminylphenol [14]).
b) inhibition of tyrosinase transcription (tretinoin, retinol, retinaldehyde, N-acetylglucosamine, glucosamine [18]).
c) inhibition of melanosome transport (linoleic acid [18]).
d) reduction of melanosome transport (niacinamide, retinoids, soy trypsin inhibitor [14]).
e) interaction with copper (L-ascorbic acid, kojic acid [14]).
f) acceleration of epidermal turnover (vitamin C, vitamin E, thioacetic acid, lactic acid, salicylic acid, liquiritin [18] glycolic acid, retinoids [14,18]).
g) inhibition of melanosome maturation (arbutin, deoxyarbutin [14]).
h) Oxidation - breakdown of melanin (lignin peroxidase [14]).
i) anti-inflammatory properties (soy milk, niacinamide [18]).
j) free radical scavenging (topical steroids, glycyrrhetinic acid [18]).

The list of whitening agents includes many more than those mentioned above. It has been proven in many cases that the combination of different agents leads to increased effectiveness. Cosmetics industry has turned its efforts to research and development of new agents with improved stability within a cosmetic formulation and with an improved efficacy and side effect profile; for this reason the search is turned to new agents usually derived from natural sources or to the modification of the structure of existing agents, aiming at reducing adverse effects compared to the original ones. In addition, for better effectiveness, less adverse effects and increased transdermal absorption, entrapment systems of a whitening agent in structures such as solid lipid nanoparticles (SLNs) are being developed.

In general, some of the adverse effects of applying whitening agents include, but are not limited to, itching, dryness, skin lysis, dermatitis, melasma and hyperpigmentation of the skin, mercury poisoning, fetal toxicity in pregnant women, Cushing's syndrome, liver failure, etc. [5]. In addition, the hypopigmentation from the prolonged application of the agents leaves the skin more vulnerable to the harmful effects of UV radiation, consequently increasing the potential appearance and development of cancerous lesions [5,13]. Protection from solar radiation is imperative, both for the prevention of pigmented lesions and for the successful outcome of hyperpigmentation treatment [5, 13]. Broad-spectrum sunscreens that protect against both UVA and UVB can provide the best protection. A good broad-spectrum sunscreen product should have a protection factor of at least SPF 30 (UVB protection) and PA +++ (UVA protection) [2]. Also, the use of emollient products is recommended in case of side effects such as dryness or itching [5].

2.2. Chemical peels

According to the histological depth of peeling achieved, chemical peels are distinguished into very superficial and superficial (e.g. solutions of α-hydroxy acids, salicylic acid, tretinoin, trichloroacetic acid [10%-20%]), medium depth (e.g. solutions of pyruvic acid, trichloroacetic acid [35%]) and deep peels (e.g. phenol peel) [18]. Depending on the substances it contains, a peeling product is classified as cosmetical, if it causes only superficial exfoliation. A very superficial peeling causes destruction of the stratum corneum only, without affecting the underlying layers, a superficial (epidermal) one causes destruction of part or all of the epidermis, while a medium-depth one (papillary dermal) causes a destruction of the entire epidermis and part or the entire papillary dermis, up to the reticular layer [18]. Caution is required for medium-depth peels, while deep peels, in general, are not recommended due to the high possibility of long-term and/or permanent pigmentation changes [14].

Common side effects across all types and depths of penetration are persistent erythema (more than three weeks) and, less commonly, the possibility of infection [16]; otherside effects include burning sensation, reactivation of herpes simplex, post-inflammatory hyperpigmentation, blisters, keloids, hypertrophic scars [19].

Regarding the treatment of pigmented lesions, chemical peels achieve the removal of already existing melanin in the skin; they do not have an inhibitory effect on melanocytes or the process of melanogenesis. In general, they are used either in addition to local treatment [14,20,21] or as a standalone treatment, although synergistically they show better results [14]. Peels are also considered more effective when applied in a series of treatments [21,22] usually lasting 3 to 5 months, enhancing the penetration of topically applied whitening agents [22].

2.3. Light emitting therapy treatments

The use of light emitting devices and lasers in facial aesthetics concerns regeneration functions or selective photothermolysis. Before each use of these devices, compliance with all protection and safety rules is imperative. Regarding skin whitening, while the application of lasers requires their use by

doctors, the use of the Intense Pulsed Light (IPL) systems can be applied by aestheticians.

IPLs are high-intensity incoherent, polychromatic light emission sources and emit at a long millisecond pulse width over a wide wavelength range of 515-1200 nm [21,23,24], while lower wavelengths, typically from 515 to 755 nm, can be eliminated with various cut-off filters. At the same time, there is also I^2PL, the second generation IPL, where the wavelengths from 900 to 1200 nm are eliminated [24]. Pulse duration provides greater thermal diffusion and a reduced probability of occurrence of post-inflammatory hyperpigmentation. The emitted light is provided by a flashlamp, larger than the laser spots, which contributes to the rapid treatment of large areas [21]. The mechanism of action of IPLs is that the light energy is converted into thermal energy that causes thermal destruction of the specific targeted area. This mechanism is considered non-ablative, since the lower layers of the skin are targeted, without affecting the surface layers of the skin.

The use of IPL is approved by the Food Drug Administration for the treatment of a variety of benign pigmented and vascular lesions [20]. It has been shown to be very effective in the treatment of photodamaged pigmented lesions such as solar lentigo and generalized dyspigmentation [23]. In addition, IPL can be used as an adjunct to topical therapy to accelerate the healing of lesions [16]. It is recommended for fair-skinned people.

2.4. Dermabrasion

Dermabrasion is considered as a complementary treatment in the treatment of pigmented lesions of the face [14]. Regarding the treatment of pigmentation lesions, the method's mechanism of action depends on the removal of melanin-containing keratinocytes. It has shown success in treating melasma [20]. In general, adverse effects concerning the treatment of melasma include post-inflammatory hyperpigmentation [16,20] and color changes, appearance of enlarged pores, loss of skin texture, pruritus, formation of keloids and milia [16].

2.5. Microneedling

Microneedling is the application of active substances to the skin by piercing it with tiny needles, facilitating the transdermal absorption of the active ingredients. It is mainly used for revitalizing and toning the skin.

A promising microneedling method involves the use of a patch with hyaluronic acid microneedles infused with reduced glutathione (GSH), which gradually dissolve as the patch is applied to the skin. This method leads to enhanced absorption of glutathione through the skin, while reducing glutathione's bad smell. Hyaluronic acid presents, as a biopolymer, high biocompatibility and adjustable physicochemical properties. In addition, it also exhibits deodorizing properties, making it an ideal material for the production of the microneedles to be infused with glutathione. The use of these patches is aimed at a sustained and long-term release of substances through transdermal routes, minimizing pain [25].

3. DISCUSSION

The pharmaceutical and the cosmetic industry have grown significantly in the field of skin whitening products, with an annual financial turnover of billions of dollars and a forecast for a continuous upward trend in the coming years. On the other hand, there is also the illegal trade of unapproved and unsuitable products, dangerous to health, which has prompted the various countries to establish legal and regulatory frameworks to eliminate these products from the market. At the same time, campaigns are being promoted to inform and raise awareness among consumers and health professionals about the risks posed by the reckless use of whitening products.

Regarding the negative effects of facial dyschromia on an individual's mental health, which effects neither Aesthetics nor Dermatology can cure, the individual should realize on his own that "charm" and "beauty" are not related only to outward appearance and, also, that different standards of beauty are subjective, ephemeral and changeable. In addition, efforts should be intensified in order to prevent the ideal of the "beautiful, attractive and successful person with white and flawless skin" from being massively projected by the media, advertising campaigns and the entertainment industry, so that people whose appearance deviates from this standard should not be further burdened psychologically and marginalized.

4. CONCLUSION

Concerning the pigmented lesions of a pathological nature, one should keep in mind that if the causative factor is not eliminated, i.e. the condition itself that causes them, no skin whitening method can offer a permanent solution. On the one hand, because the skin is subject to a continuous renewal process and on the other hand, because any therapeutic method cannot be continued perpetually, but must be stopped after a certain

period of time, to avoid adverse effects and health complications and, if necessary, repeated, same or modified or completely different, in the future. Thus, one should not expect a "permanent solution", but the "best possible result". Also, it is not recommended (in fact, it is contraindicated) to apply the various skin whitening methods during the summer season, and in general during periods when there is a lot of sunshine, as the chances of complications due to exposure to sunlight radiation are large.

For the successful outcome of a treatment and for optimal results, it is necessary, both for the therapist and for the person to whom the treatment is administered, to follow all protection, safety and hygiene measures during the treatment, and, also, adherence to instructions during the post-treatment period by the treated individual himself.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Chen Y.-H., Huang L., Wen Z.-H., Zhang C., Liang C.-H., Lai S.-T., Luo L.-Z., Wang Y.-Y., Wang G.-H.: "Skin whitening capability of shikimic acid pathway compound". *Eur Rev Med Pharmacol Sci.* 20(6): 1214-1220 (2016).

2. Aurangabadkar S.J.: "Optimizing Q-switched lasers for melasma and acquired dermal melanoses". *Indian J DermatoI VenereoILeproI. 85*: 10-17 (2019). **https://doi.org/10.4103/ijdvl.IJDVL_1086_16**

3. Plensdorf S., Livieratos M., Dada N.: "Pigmentation Disorders: Diagnosis and Management". *Am Fam Physician.* 96(12):797-804 (2017).

4. Goel A.: "Clinical applications of Q-switched NdYAG 1064 nm Laser". *Indian J Dermatol VenereolLeprol.* 74: 682-6 (2008). **doi: 10.4103/0378-6323.45135**

5. Arbab A. H. H., Mudawi M. M. E.: "Review on Skin Whitening Agents". *Khartoum Pharmacy Journal.* 13(1): 5-9 (2010).

6. Jeon G., Kim C., Cho U.M., Hwang E.T., Hwang H.S., Min J.: "Melanin-Decolorizing Activity of Antioxidant Enzymes, Glutathione Peroxidase, Thiol Peroxidase, and Catalase". *Mol Biotechnol.* 63(2): 150-155 (2021). **https://doi.org/10.1007/s12033-020-00292-6**

7. Panzella L., Napolitano A.: "Natural and Bioinspired Phenolic Compounds as Tyrosinase Inhibitors for the Treatment of Skin Hyperpigmentation: Recent Advances". *Cosmetics.* 6(4): 57 (2019). **https://doi.org/10.3390/cosmetics6040057**

8. Gatea A. H.: "Review on analysis of interesting whitening agents in cosmetics products". *IOP Conf. Ser.: Mater. Sci. Eng.* 928 052001 (2020). **https://doi.org/10.1088/1757-899X/928/5/052001**

9. Watanabe F., Hashizume E., Chan G. P., Kamimura A.: "Skin-whitening and skin-condition-improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women". *Clin CosmetInvestig Dermatol. 7*: 267-74 (2014). **https://doi.org/10.2147/CCID.S68424**

10. Markiewicz E., Idowu O.C.: "Melanogenic Difference Consideration in Ethnic Skin Type: A Balance Approach Between Skin Brightening Applications and Beneficial Sun Exposure". *Clin CosmetInvestig Dermatol.* 13: 215-232 (2020). **https://doi.org/10.2147/CCID.S245043**

11. Pillaiyar T., Manickam M., Namasivayam V.: "Skin whitening agents: medicinal chemistry perspective of tyrosinase inhibitors". *Journal of enzyme inhibition and medicinal chemistry.* 32(1): 403-425 (2017). **https://doi.org/10.1080/14756366.2016.1256882**

12. Sadaqat B., Khatoon N., Malik A.Y., Jamal A., Farooq U., Ali M. I., He H., Liu F.-J., Guo H., Urynowicz M., Wang Q., Huang Z.: "Enzymatic decolorization of melanin by lignin peroxidase from *Phanerochaetechrysosporium*". *Sci Rep.* 10(1): Article number: 20240 (2020). **https://doi.org/10.1038/s41598-020-76376-9**

13. Burger P., Landreau A., Azoulay S., Michel T., Fernandez X.: "Skin Whitening Cosmetics: Feedback and Challenges in the Development of Natural Skin Lighteners". *Cosmetics.* 3(4): Article number: 36 (2016). **https://doi.org/10.3390/cosmetics3040036**

14. Vashi N.A., Kundu R.V.: "Facial hyperpigmentation: causes and treatment". *British Journal of Dermatology. 169 (Suppl. 3)*:41–56 (2013). **https://doi.org/10.1111/bjd.12536**

15. Smit N., Vicanova J., Pavel S.: "The Hunt for Natural Skin Whitening Agents". *Int. J. Mol. Sci.10*: 5326-5349 (2009). **https://doi.org/10.3390/ijms10125326**

16. Gupta A. K., Gover M. D., Nouri K., Taylor S.: "The treatment of melasma: A review of clinical trials". *J Am Acad Dermatol. 55(6)*:1048 – 1065 (2006). **https://doi.org/10.1016/j.jaad.2006.02.009**

17. Gillbro J. M., Olsson M. J.: "The melanogenesis and mechanisms of skin-lightening agents – existing and new approaches*". Int J Cosmet Sci. 33(3)*: 210-21 (2011). **https://doi.org/10.1111/j.1468-2494.2010.00616.x**

18. Couteau C., Coiffard L.: "Overview of Skin Whitening Agents: Drugs and Cosmetic Products", *Cosmetics. 3(27)*: 1-16 (2016). **https://doi.org/10.3390/cosmetics3030027**

19. Davis E. C., Callender V. D.: "Postinflammatory Hyperpigmentation: A Review of the Epidemiology, Clinical Features, and Treatment Options in Skin of Color". *J Clin Aesthet Dermatol.* 3(7): 20–31 (2010).

20. Bagherani N., Gianfaldoni S., Smoller B.: “An Overview on Melasma”. *Pigmentary Disorders. 2,* Issue 10: 1-18 (2015).
https://doi.org/10.4172/2376-0427.1000216

21. Trivedi M.K., Yang F.C., Cho B.K.: “A review of laser and light therapy in melasma”. *International Journal of Women’s Dermatology* 3(1): 11-20 (2017).
https://doi.org/10.1016/j.ijwd.2017.01.004

22. Woolery-Lloyd H., Kammer J.N.: “Treatment of Hyperpigmentation”. *SeminCutan Med Surg. Elsevier Inc. 30*: 171-175 (2011).
https://doi.org/10.1016/j.sder.2011.06.004

23. Dierickx C. C.: “Laser Treatment of Pigmented Lesions”. *Laser Dermatology, Springer, Berlin, Heidelberg.* Ch. 3: 37 – 60 (2005).
https://doi.org/10.1007/3-540-27205-4_3

24. Patil U. A., Dhami L. D.: “Overview of lasers”. *Indian J Plast Surg Supplement.*41: 101 –113 (2008).

25. Lee Y., Kumar S., Kim S.H., Seong K.-Y., Lee H., Kim C., Jung Y.-S., Yang S.Y.: “Odorless Glutathione Microneedle Patches for Skin Whitening”. *Pharmaceutics.* 12(2): 100 (2020).
https://doi.org/10.3390/pharmaceutics12020100