دکتر منصور نصیری کاشانی

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و جذام دانشگاه علوم پزشکی تهران

Facial Hyperpigmentation

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Center for Research and Training in
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Facial Hyperpigmentation

- Melasma
- Riehl melanosis (Pigmented cosmetic dermatitis)
- Poikiloderma of Civatte (Erythromelanosis interfollicularis)
- Erythromelanosis follicularis faciei et colli
- Peribuccal pigmentation of Brocq
- Berloque dermatitis
- Erythema dyschromicum perstans (Ashy dermatosis)
- Lichen planus pigmentosus
- Drug-induced hyperpigmentation
- Post inflammatory Hyperpigmentation

Melasma

- Melasma is a common, chronic, and recurring disorder of hyperpigmentation arising from hyperfunctional melanocytes that deposit excessive amounts of melanin in the epidermis and dermis
- Melasma is particularly common in women, especially those of reproductive age, and in body areas with high amounts of sun exposure, notably the face

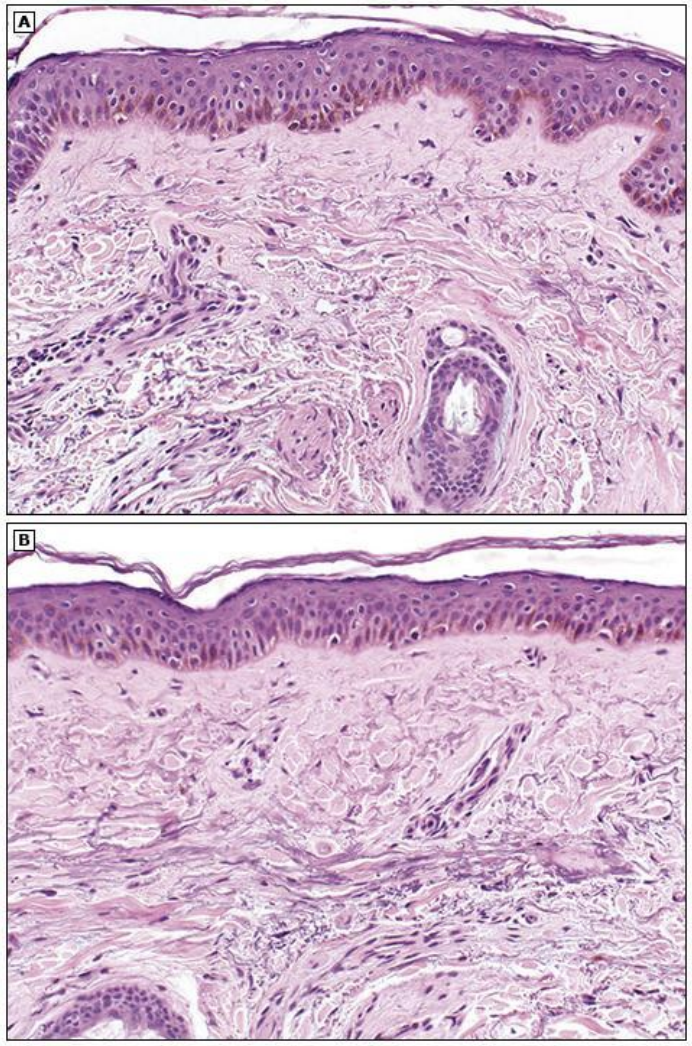
Melasma

RISK AND TRIGGER FACTORS:

- Genetic predisposition
- Exposure to sunlight (UV and visible light)
- Skin phototype
- Hormonal factors (pregnancy, hormonal therapies, oral contraceptives)
- Cosmetics
- Medicines (eg, photosensitizing drugs and anticonvulsants)
- Zinc deficiency

PATHOLOGY

- Hyperactive melanocytes without hyperplasia
- Similar melanocyte number in lesional and perilesional skin
- Larger melanocytes, more melanosomes and prominent dendrites
- Keratinocytes with increased number of melanosomes
- Disruption to the basement membrane
- Lymphohistiocytic infiltrates
- Dermal elastosis
- Increased vascularization



PATHOGENESIS

- **Genetics:** polygenic inheritance
- **Hormones**: oral contraceptive, pregnancy, menopause (for extrafacial involvement) and hormonal replacement therapy
- **Barrier function and oxidative stress:** Chronic UV exposure reduces synthesis of epidermal free fatty acids and triglycerides, which are important in maintaining the skin's barrier function.
- **Neural involvement:** Melasma lesions often follow the path of the trigeminal nerves, which implies a neural component to the pathogenesis

International Journal of Dermatology

Review

Melasma and thyroid disorders: a systematic review and meta-analysis

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Abstracts

Background Thyroid hormones may play a key role in melasma; however, melasma link with thyroid disorders remains controversial.

Objectives To compare the serum levels of thyroid-stimulating hormone (TSH), T4, T3, anti-thyroid peroxidase (anti-TPO), and antithyroglobulin between patients with melasma and control group using meta-analysis.

Methods We screened 10 databanks and search engines, searched mesh and nonmesh terms. The identified evidences were reviewed and quality assessed using the Newcastle-Ottawa Scale (NOS). The heterogeneity between the primary results was investigated using Cochrane and *I*-square indices. Random effect model was applied to combine the standardized mean differences of thyroid function indicators between patients with and without melasma. *P* values meta-analysis was used to investigate the association between anti-TPO and melasma.

Results We included seven studies, 473 cases, and 379 controls that had been investigated. The total standardized mean differences (95% confidence intervals) of TSH, T3, T4, and antithyroglobulin antibody between cases and controls were estimated to be 0.33 (0.18, 0.47), −0.01 (−0.20, 0.19), −1.50 (−2.96, −0.04), and 0.62 (0.14, 1.11), respectively. The corresponding figures among women were 0.35 (0.17, 0.52), 0.10 (−0.17, 0.38), −2.75 (−6.30, 0.81), and 0.99 (0.14, 1.83), respectively. *P* value of meta-analysis showed a significant relationship between anti-TPO serum level and melasma (Fisher = 26.80, *P* = 0.020).

Conclusion Serum levels of TSH, anti-TPO, and antithyroglobulin antibody were significantly higher in patients with melasma than those without melasma. Moreover, these differences were more severe among women with melasma.

What is new?

- Melasma is an acquired type of hyperpigmentation and might be associated with thyroid disorders.
- Results of the present study showed that serum levels of TSH, anti-thyroid peroxidase (anti-TPO), and antithyroglobulin antibody were significantly higher in patients with melasma than those without melasma. Moreover, these differences were more severe among women with melasma.
- Serum levels of TSH, anti-TPO, and antithyroglobulin antibodies are associated with melasma, especially among women.

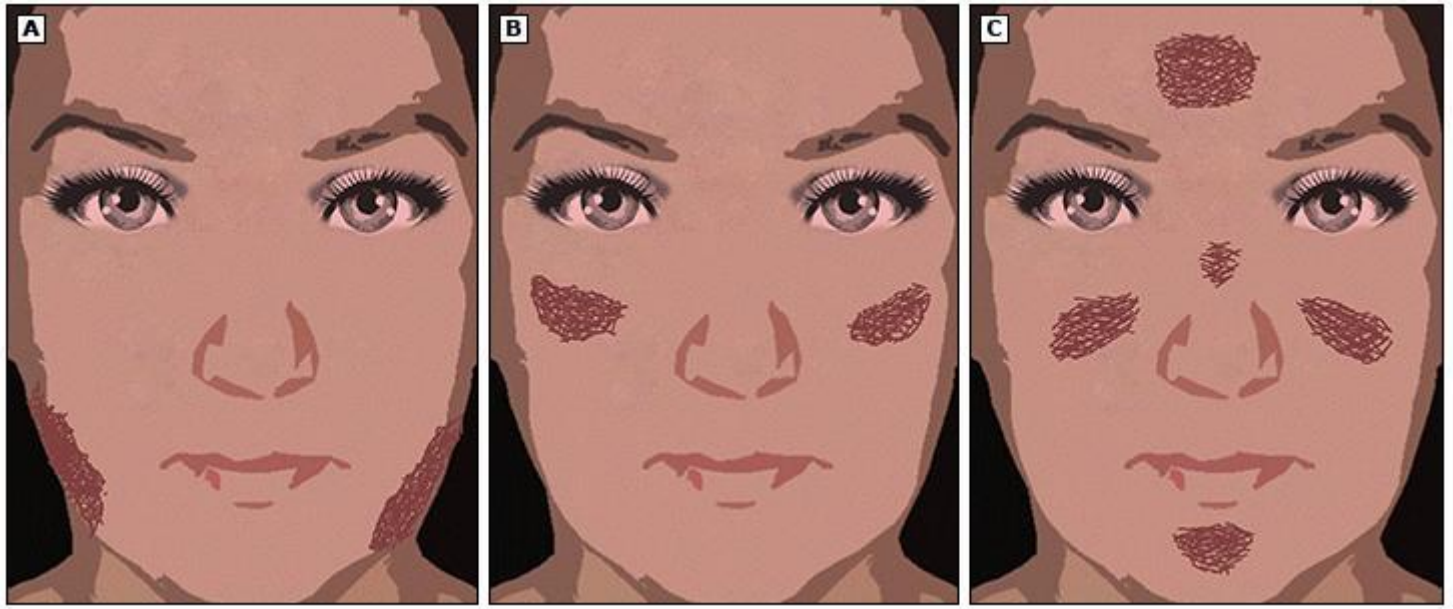
Introduction

Melasma is an acquired type of hyperpigmentation that is displayed as asymptomatic symmetric reddish-brown or gray-blue macules or patches mainly localized in the sun-exposed body areas, namely chin, cheek, forehead, and upper lip.[1–4] As the

- We included seven studies, 473 cases, and 379 controls that had been investigated.
- Serum levels of TSH, anti-TPO, and antithyroglobulin antibody were significantly higher in patients with melasma than those without melasma.
- Moreover, these differences were more severe among women with melasma.

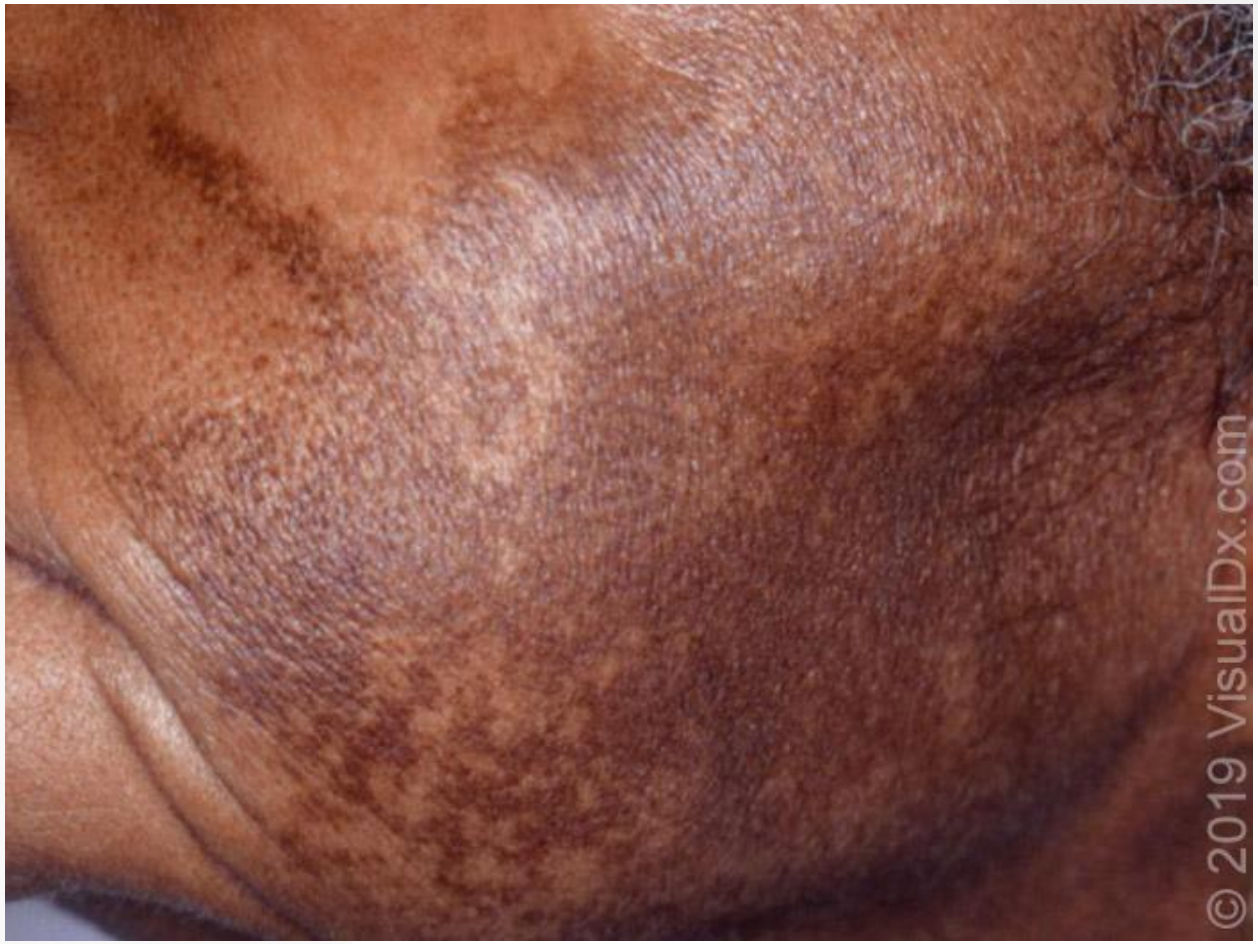
CLINICAL PRESENTATION

- A: Mandibular
- B: Malar
- C: Centrofacial



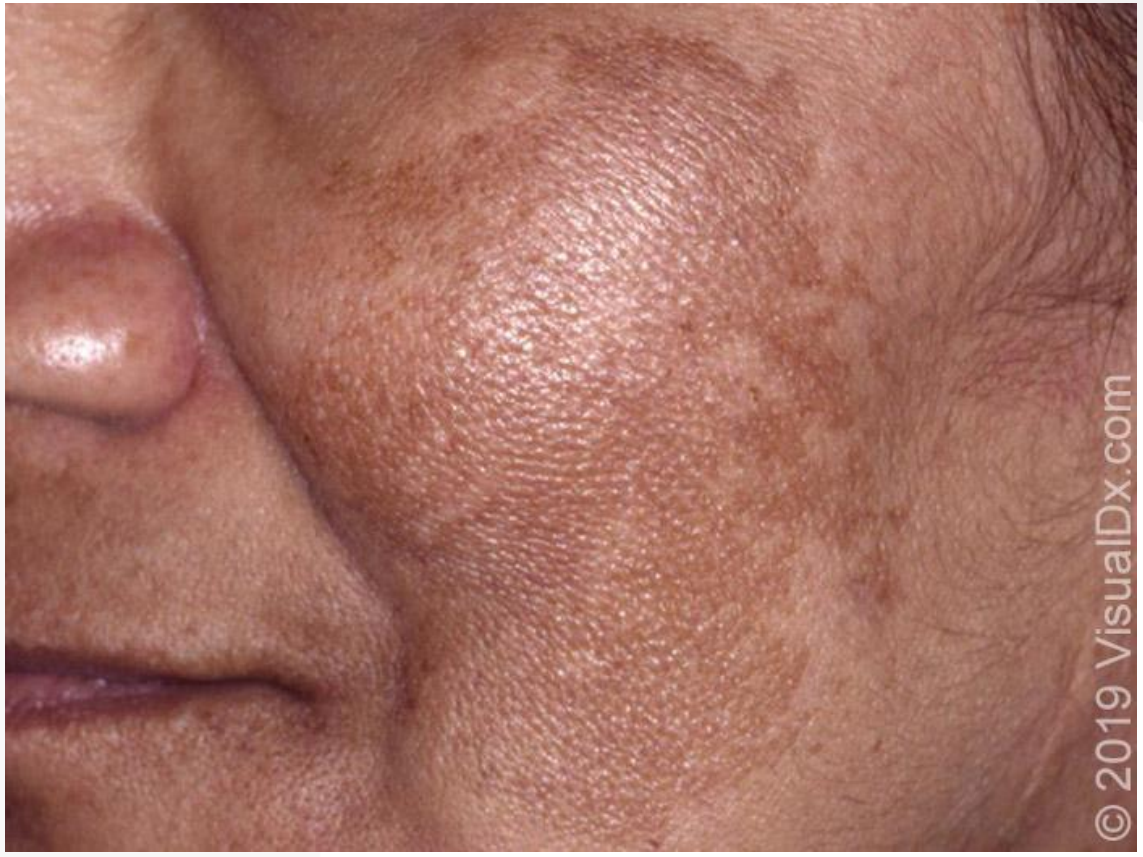
Mandibular

- Lower jawline



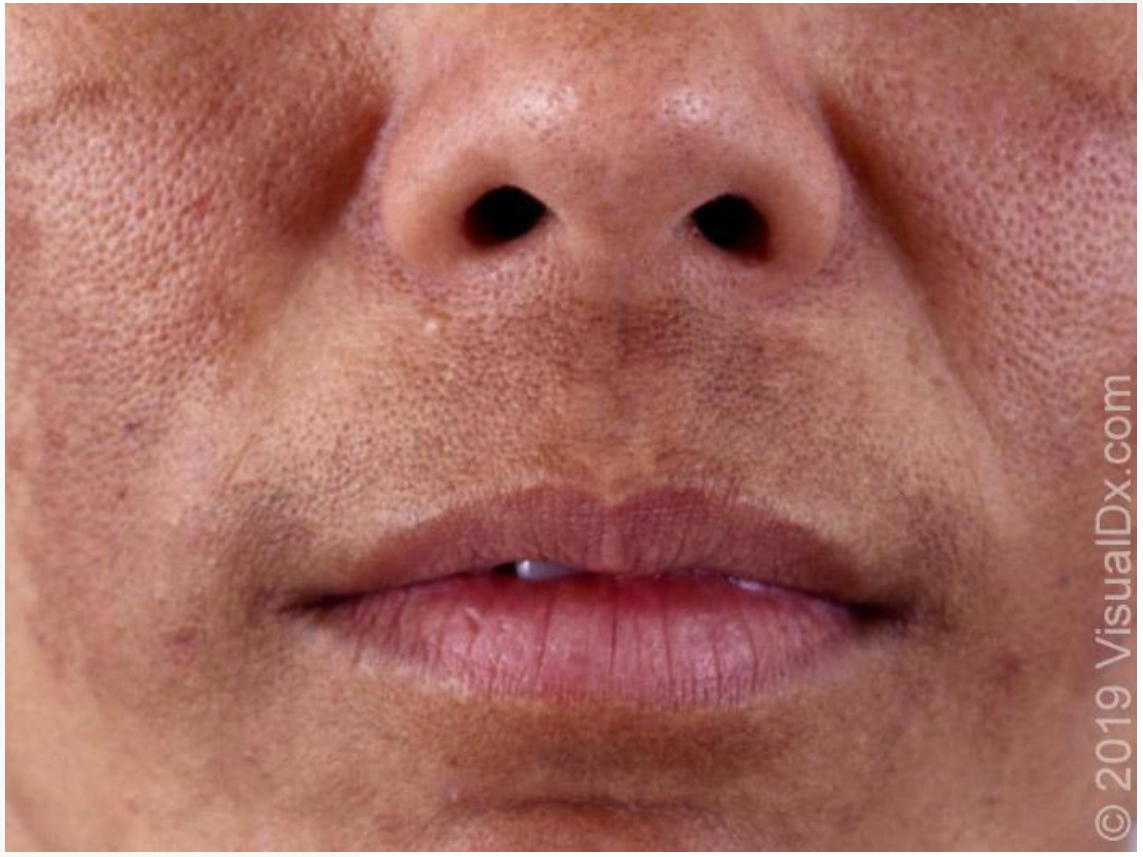
Malar

- lateral cheek



Centro facial

- Forehead
- Cheeks
- Nose
- Upper lip
- Chin



Extra facial Melasma

- Arms (95 percent)
- Forearms (80 percent)
- Chest (47 percent)
- Back (11 percent)

Riehl melanosis (Pigmented cosmetic dermatitis)

- A distinctive pattern of grey-brown facial pigmentation was first described by Riehl in Vienna between 1916 and 1920.
- Riehl attributed this pigmentation to contact with noxious substances or to wartime living conditions.
- It was subsequently reported from other parts of the world.
- Pigmented cosmetic dermatitis-like (Riehl's melanosis-like) pigmentation has been reported in patients with primary Sjogren's syndrome.

Riehl melanosis
(Pigmented cosmetic dermatitis)

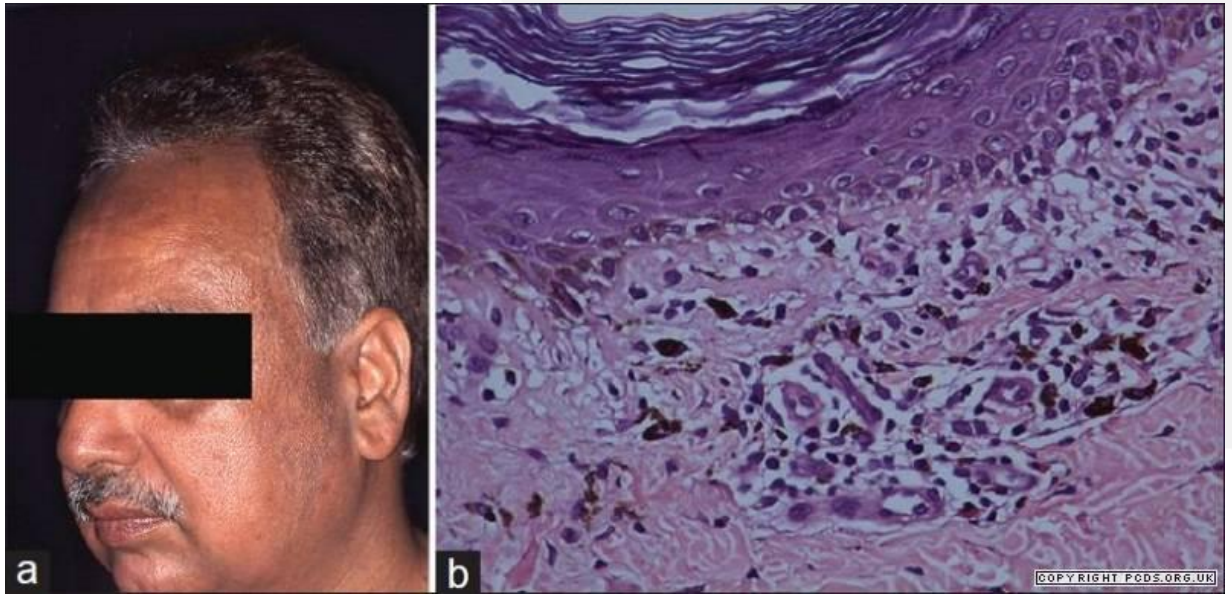
- Middle age women
- Predisposing factors:
  - Tar derivatives
  - Fragrances
  - Cosmetic ingredients

Riehl melanosis (Pigmented cosmetic dermatitis)

- Clinical features:
  - Brownish-grey pigmentation more intense on the forehead and temples.
  - The pigmentation may extend to the other parts of body.
  - Horny plugs fill the follicles and there may be some scaling.

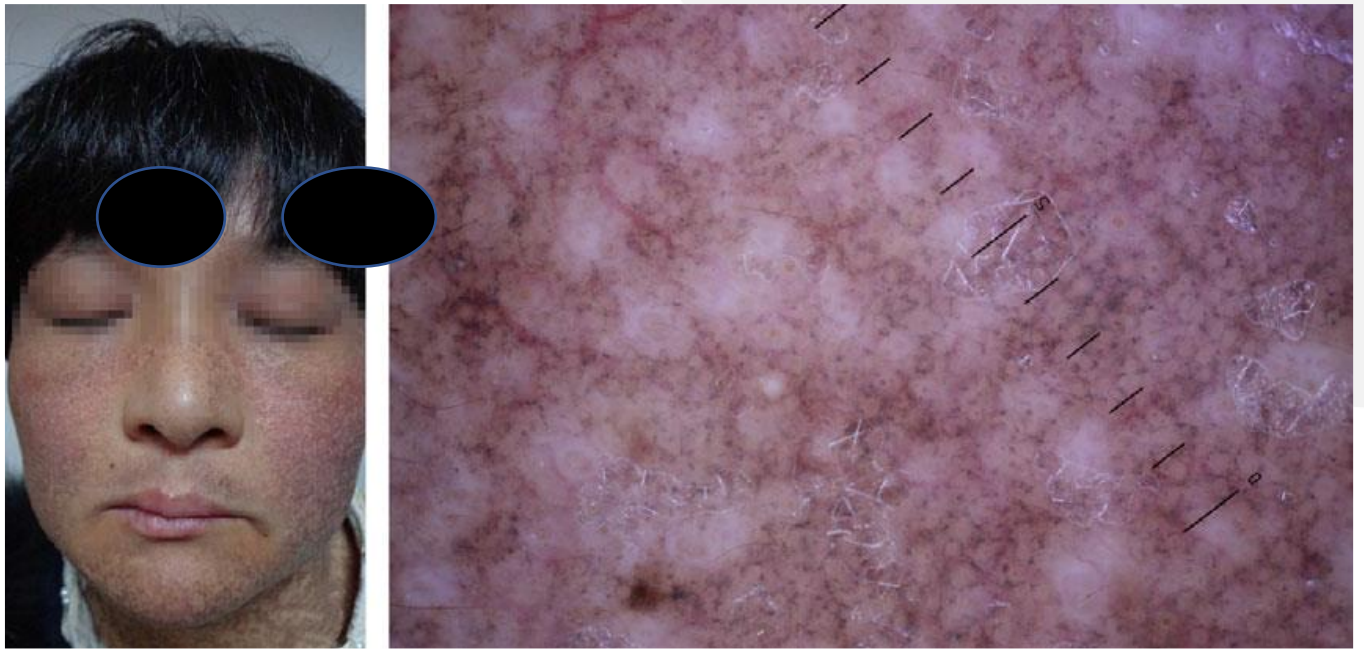
Riehl melanosis
(Pigmented cosmetic dermatitis)

- Pathology:
  - Liquefaction degeneration of the basal layer
  - Perivascular or band-like dermal infiltrate
  - Pigmentary incontinence (in the early stages)
  - Many melanophages in the upper dermis (in late stages)



Riehl melanosis
(Pigmented cosmetic dermatitis)

- Dermoscopy:
  - slight scales
  - pseudonetwork
  - grey dots/granules
  - follicular keratotic plugs
  - perifollicular whitish halo
  - telangiectatic vessels



Riehl melanosis (Pigmented cosmetic dermatitis)

- Diagnosis:
  - Patch testing

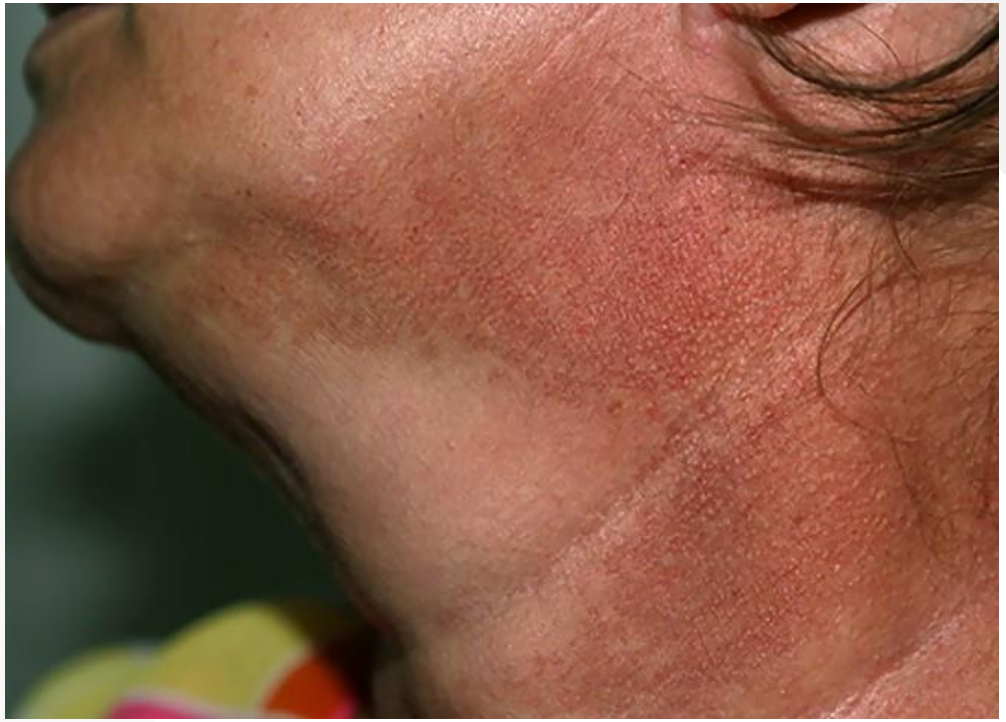
- Treatment:
  - Where a contact cause can be identified, it should be avoided.
  - Sun protection
  - Hydroquinone 2–5% plus tretinoin or glycolic acid
  - Intense pulse light (IPL) and Q-switch Nd:YAG laser

Poikiloderma of Civatte
(Erythromelanosis interfollicularis)

- This characteristic pattern of reticulate hyperpigmentation of the face and neck was first reported in 1923 by Civatte.
- It usually presents as a triad of atrophy, telangiectasia, hyper- and hypopigmentation, which typically appears on the sides of the face and neck and on the upper anterior chest after years of repeated UV exposure.

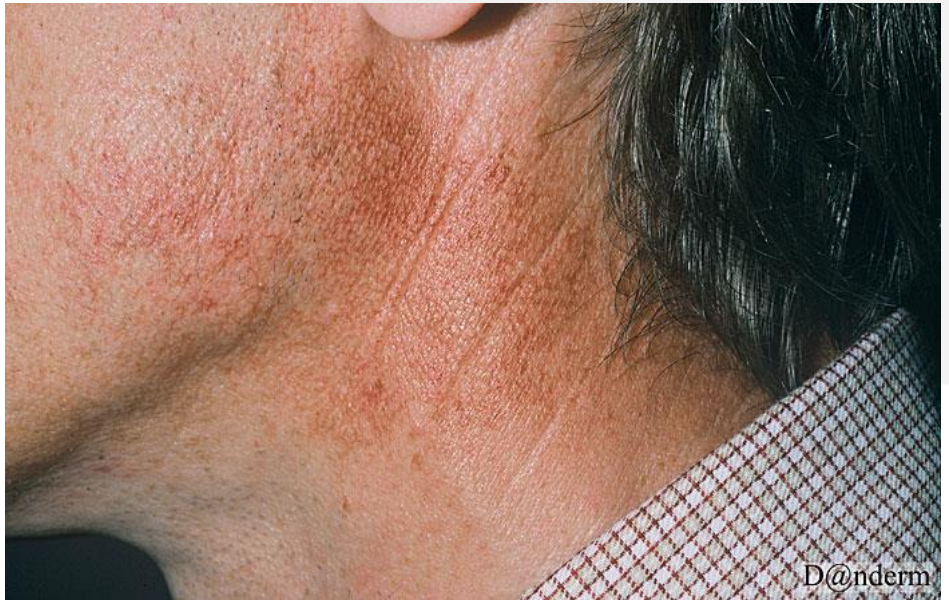
Poikiloderma of Civatte (Erythromelanosis interfollicularis)

- More common in fair skin, middle age, women
- **Predisposing factors**
  - Exposure to light
  - Phototoxic or photoallergic substances in cosmetics



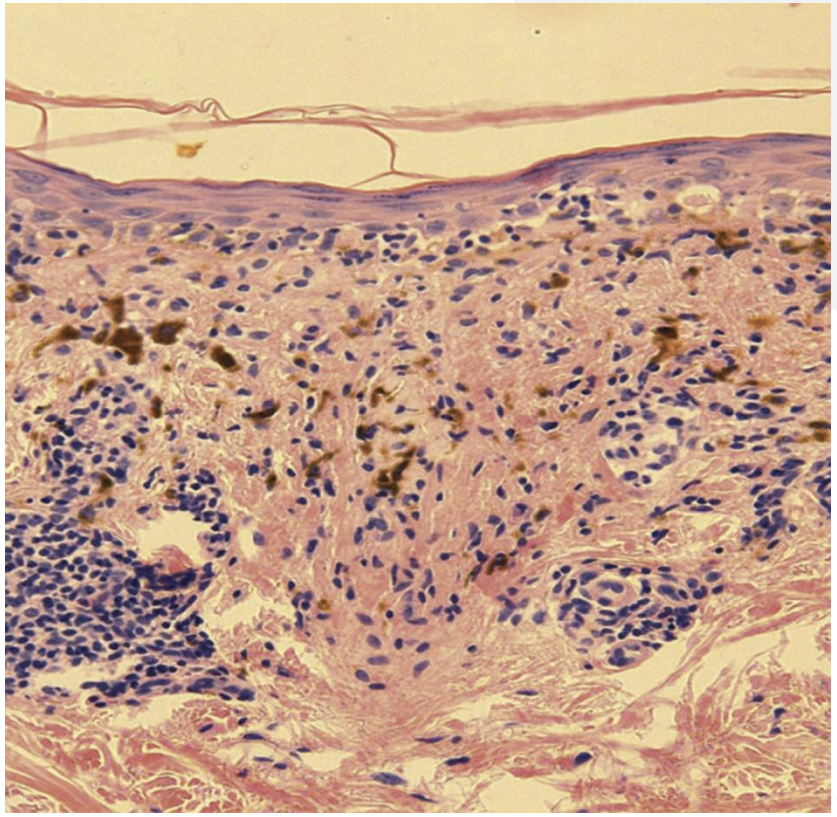
Poikiloderma of Civatte
(Erythromelanosis interfollicularis)

- Clinical features:
  - It develops symmetrically on the sides of the face, neck and upper aspect of the chest
  - The submandibular and submental areas are spared thus implicating sunlight in the pathogenesis of this condition.
  - It is mostly asymptomatic, although some patients experience itching, burning and flushing.



Poikiloderma of Civatte
(Erythromelanosis interfollicularis)

- Pathology:
  - Thinning of epidermis
  - Hydropic degeneration of the basal cell layer
  - Melanophages in the papillary dermis
  - Dilatation of the papillary dermal capillaries



Poikiloderma of Civatte
(Erythromelanosis interfollicularis)

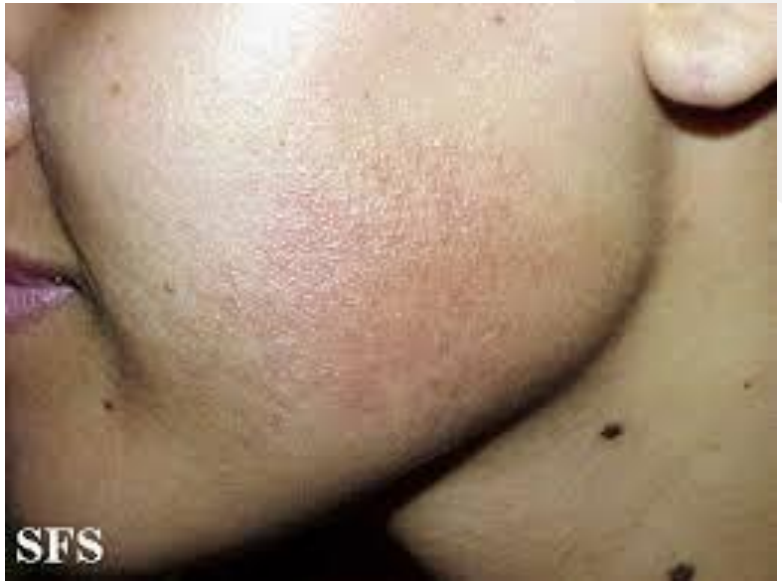
- Diagnosis:
  - Patch testing can be useful if induction by allergen is suspected.
- **Treatment:**
  - Photoprotection with a high SPF sunscreen
  - Avoiding perfumes
  - Intense pulsed light
  - Tunable dye laser
- It is slowly progressive and irreversible.

Erythromelanosis follicularis faciei et colli

- This syndrome, of unknown origin, was originally described in Japan by Kitamura *et al*. in 1960.
- **Age**
  - Peak age of onset in the second decade of life.
- **Sex**
  - Affects both sexes.
- **Ethnicity**
  - Affects all races, but more frequent in Asians.
- **Associated diseases**
  - May be associated with keratosis pilaris
- **Genetics**
  - Few familial cases have been reported.

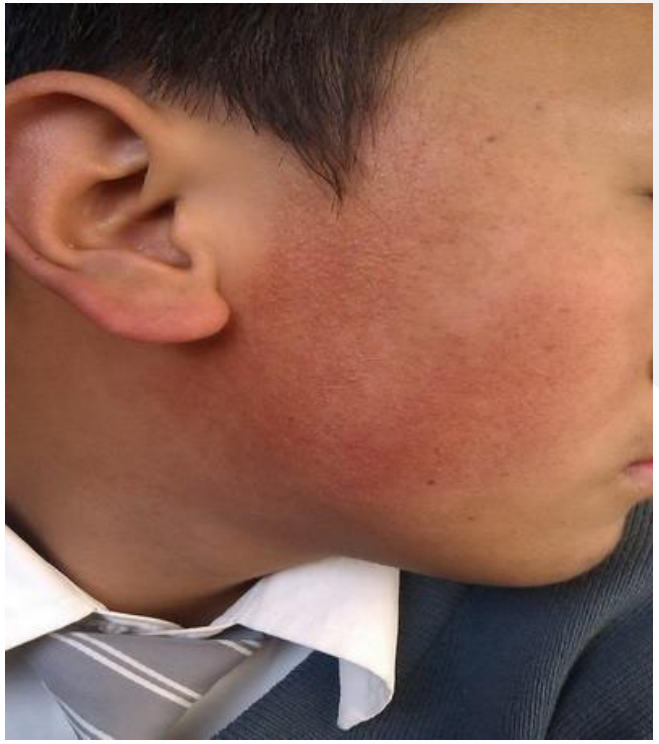
Erythromelanosis follicularis faciei et colli

- Clinical features:
  - It is characterized by a triad of hyperpigmentation, follicular plugging and erythema, with or without telangiectasia, affecting the lateral aspects of the cheeks and in some cases the neck.



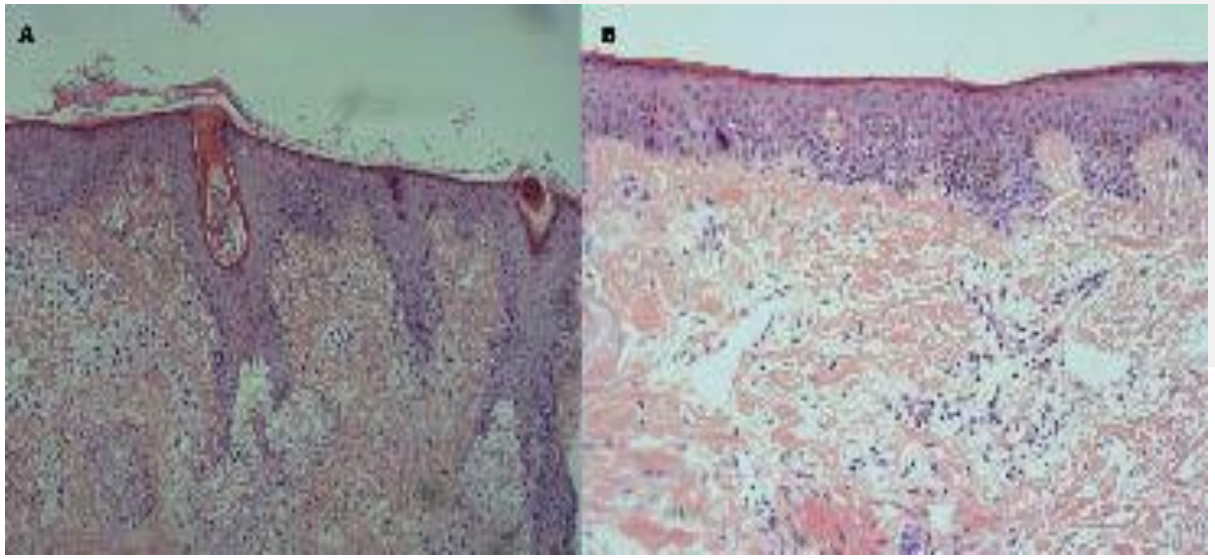
Erythromelanosis follicularis faciei et colli

- Clinical features:
  - The majority of affected vellus hairs are lost, but terminal hair follicles of the scalp and beard are usually not affected.
  - The distribution, and lack of clinical follicular keratosis, or scarring readily distinguish it from other forms of keratosis pilaris and from other facial melanoses.



Erythromelanosis follicularis faciei et colli

- **Pathology**
  - Slight hyperkeratosis and hyperpigmentation of the basal layer.
  - The hair follicles are enlarged and contain lamellar horny masses (follicular plug).
  - The epidermis overlying the affected follicle is flattened and contains excess melanin.
  - In the dermis, lymphocytic infiltrate surrounds dilated vessels.



Erythromelanosis follicularis faciei et colli

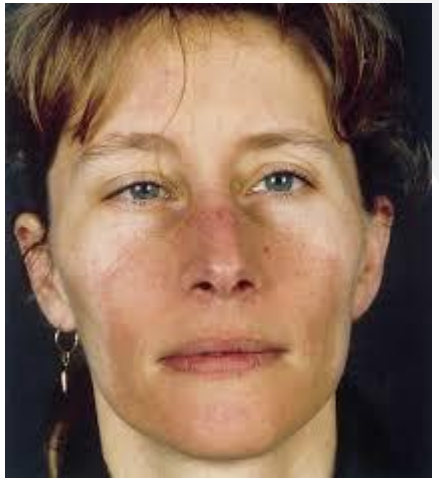
- Treatment:
  - It spreads slowly, is persistent and response to therapy is generally poor and prone to relapse.
  - Avoidance of solar exposure and use of sunscreen is recommended.
  - Topical keratolytic: urea cream (10–20%), ammonium lactate lotion (12%), tretinoin cream (0.05–0.1%)
  - Metronidazole cream, tacalcitol cream
  - Salicylic acid peels and glycolic acid peels
  - Oral Isotretinoin (0.1–1 mg/kg/day)
  - Laser treatment (PDL) of the background erythema

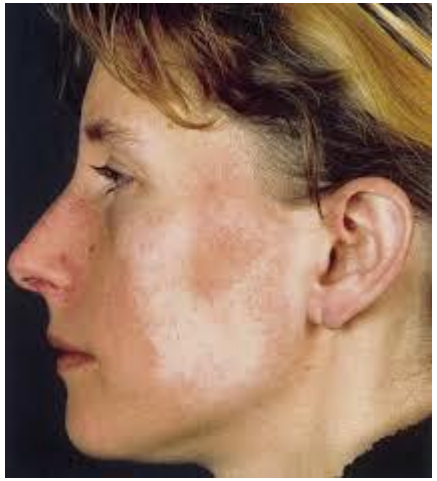
Peribuccal pigmentation of Brocq

- It was Brocq in 1923 who first reported a case of perioral hyperpigmentation in a unique clinical pattern.
- Predominantly in middle-aged women and has only rarely been reported in men.
- A photodynamic substance in cosmetics is probably responsible.

Peribuccal pigmentation of Brocq

- Clinical features:
  - Diffuse brownish-red pigmentation develops symmetrically around the mouth but spares a narrow perioral ring.
  - It may extend up the center of the face to the forehead and in some cases there are well-defined patches of pigmentation over the angles of the jaw and the temples.





Peribuccal pigmentation of Brocq

- Treatment:
  - The erythematous component, and the intensity of the pigmentation, may fluctuate over short periods.
  - The pigmentation is usually persistent but tends to fade gradually if the cause is eliminated.

Berloque dermatitis

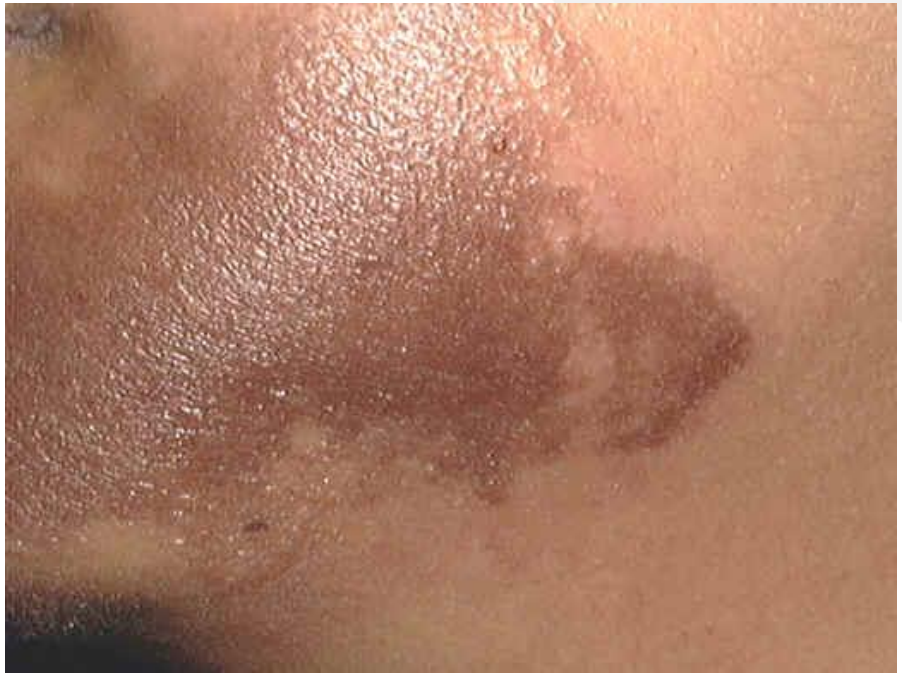
- Skin pigmentation due to phototoxic reaction to perfumes applied to the skin.
- It can be seen in any age, any sex, and any racial group.
- It results from the UV-stimulated melanogenesis by 5-methoxypsoralen (bergapten) in perfumes containing bergamot oil.

Berloque dermatitis

- The reaction occurs in only a small proportion of those exposed and depends on:
  - The readiness with which the bergapten is absorbed,
  - The quantity applied,
  - The intensity and duration of exposure to UV light.

Berloque dermatitis

- **Clinical features:**
  - Deep-brown pigmentation follows the pattern formed by droplets of perfume over the skin from their points of application and then fades after weeks or months.



Erythema dyschromicum perstans (Ashy dermatosis)

- This clinical syndrome of unknown origin was first reported by Ramirez of El Salvador in 1957 under the term ‘los cenicientos’ (the ashy ones) due to the ashy discoloration of the skin.
- A further case series was reported by Convit, Kerdel-Vegas and Rodriguez from Venezuela in 1961 who commented on the presence of raised erythematous borders in the early stages and proposed the term ‘erythema dyschromicum perstans’ .
- It has been proposed that ashy dermatosis be used for all such cases but that erythema chronicum perstans be limited to those cases in which an inflammatory phase with erythema has been observed.

Erythema dyschromicum perstans (Ashy dermatosis)

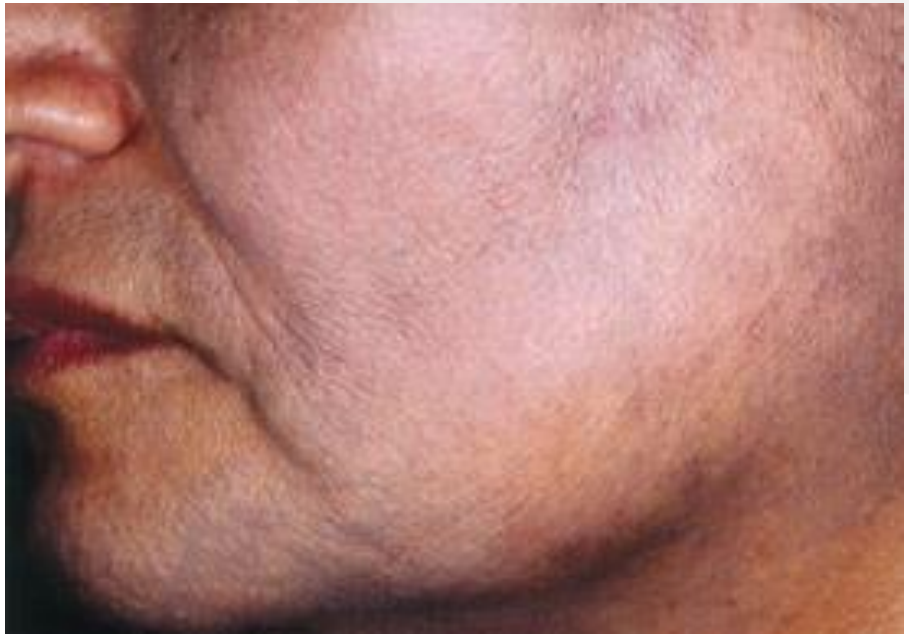
- **Age**
  - From childhood to old age, most frequently in young adults.
- **Sex**
  - It occurs in both sexes, but females more than males.
- **Ethnicity**
  - Mainly observed in intermediate skin types. Most published cases have been from Central and South America or East Asia.

Erythema dyschromicum perstans (Ashy dermatosis)

- Pathomechanism:
  - Still unknown.
  - Parasite infection
  - Chemicals such as ammonium nitrate and barium sulfate
  - Environmental allergens
- An immunological response to any of these factors might define the extent of lesional inflammation of the skin based on the genetic profile, i.e., a strong inflammatory reaction against these factors might lead to EDP, where-as a mild reaction might lead to AD.

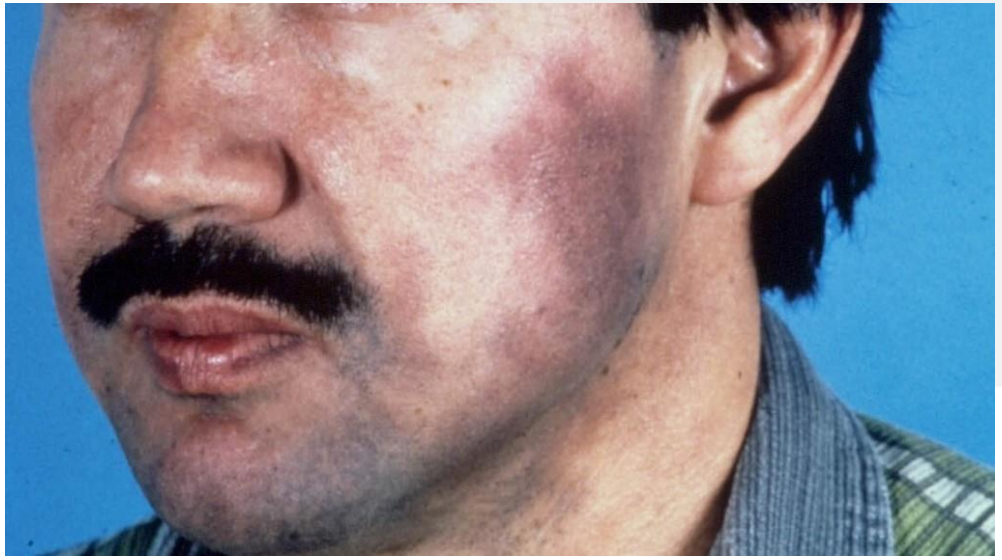
Erythema dyschromicum perstans (Ashy dermatosis)

- **Clinical features**
  - It is characterized by numerous macules of varying shades of grey.
  - There may initially be signs of inflammation with a red, slightly raised and palpably infiltrated margin (erythema dyschromicum perstans).



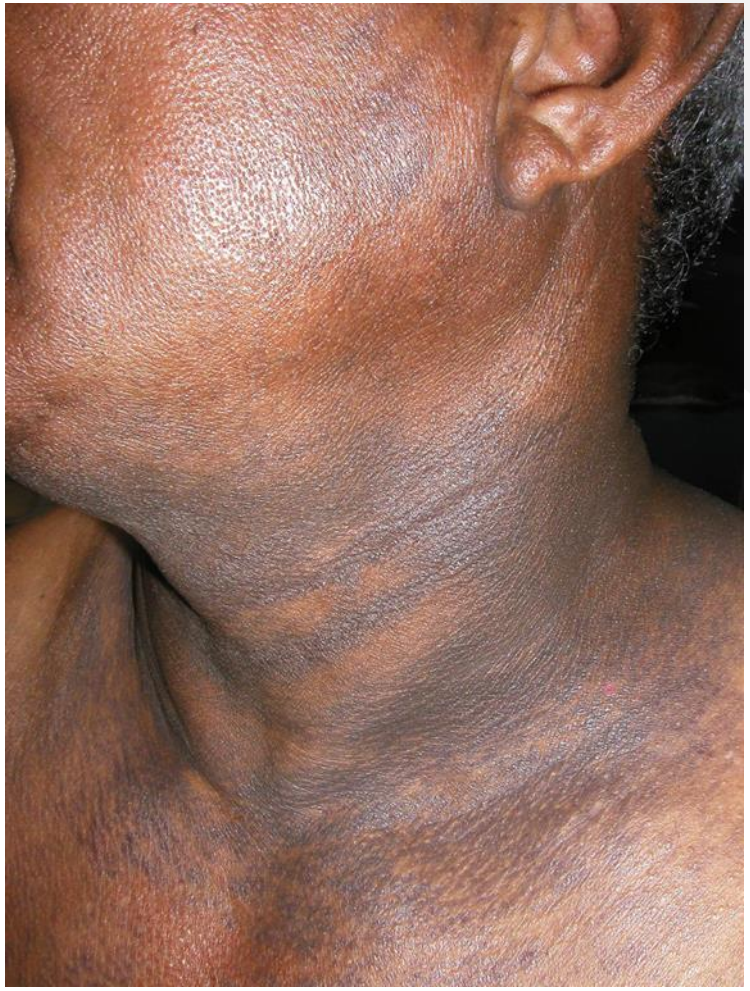
Erythema dyschromicum perstans (Ashy dermatosis)

- In a recent review of 68 patients from Korea, less than a fifth were observed to have peripheral erythematous borders to their lesions.
- In this study, the trunk was affected in two-thirds and the face in one-third of patients.
- The erythematous halo was associated with only 17.3% of patients.



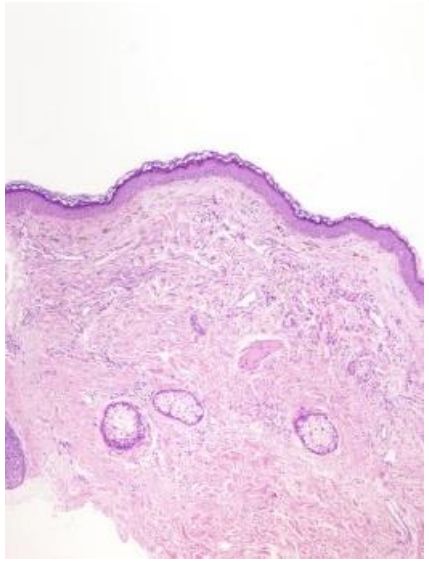
Erythema dyschromicum perstans (Ashy dermatosis)

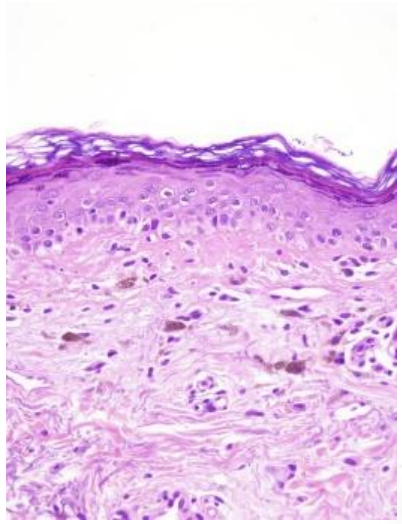
- **Clinical features**
  - The macules vary in size and tend to coalesce over extensive areas of the trunk, limbs and face.
  - Against the general greyish background are macules of hypomelanosis or hypermelanosis.
  - The lesions are mostly asymptomatic, although some patients may experience mild pruritus.
  - Mucous membranes are spared.



Erythema dyschromicum perstans (Ashy dermatosis)

- **Pathology**
  - The active border shows vacuolar degeneration of the basal cells and epidermis contains much pigment and there is pigmentary incontinence.
  - The dermal vessels are sleeved with an infiltrate of lymphocytes and histiocytes, and there are many melanophages.





Erythema dyschromicum perstans (Ashy dermatosis)

- **Treatment:**
  - There is no consistently effective treatment and the initial erythematous phase tends to settle after several months and the pigmentation is persistent with a tendency to extend gradually over years.
  - Camouflage creams and make-up
  - Clofazimine 100 mg/day for 3 months in inflammatory cases (response rate of 66–87%)
  - Dapsone 100 mg/day for 3 months
  - Oral corticosteroid therapy
  - UV therapy
  - Fractionated non-ablative treatment sessions utilizing the 1,550 nm erbium-doped fiber laser in combination with topical tacrolimus ointment
  - Rarely spontaneous resolution over several years after has been reported.

Lichen planus pigmentosus

- A rare variant of lichen planus that occurs predominantly in individuals with darker skin phototypes (III to V)

- It generally affects young to middle-aged adults, especially those from India, Latin America, and the Middle East.

- Photodistribution suggests that ultraviolet (UV) light may play a role in the pathogenesis of LPP.

Lichen planus pigmentosus

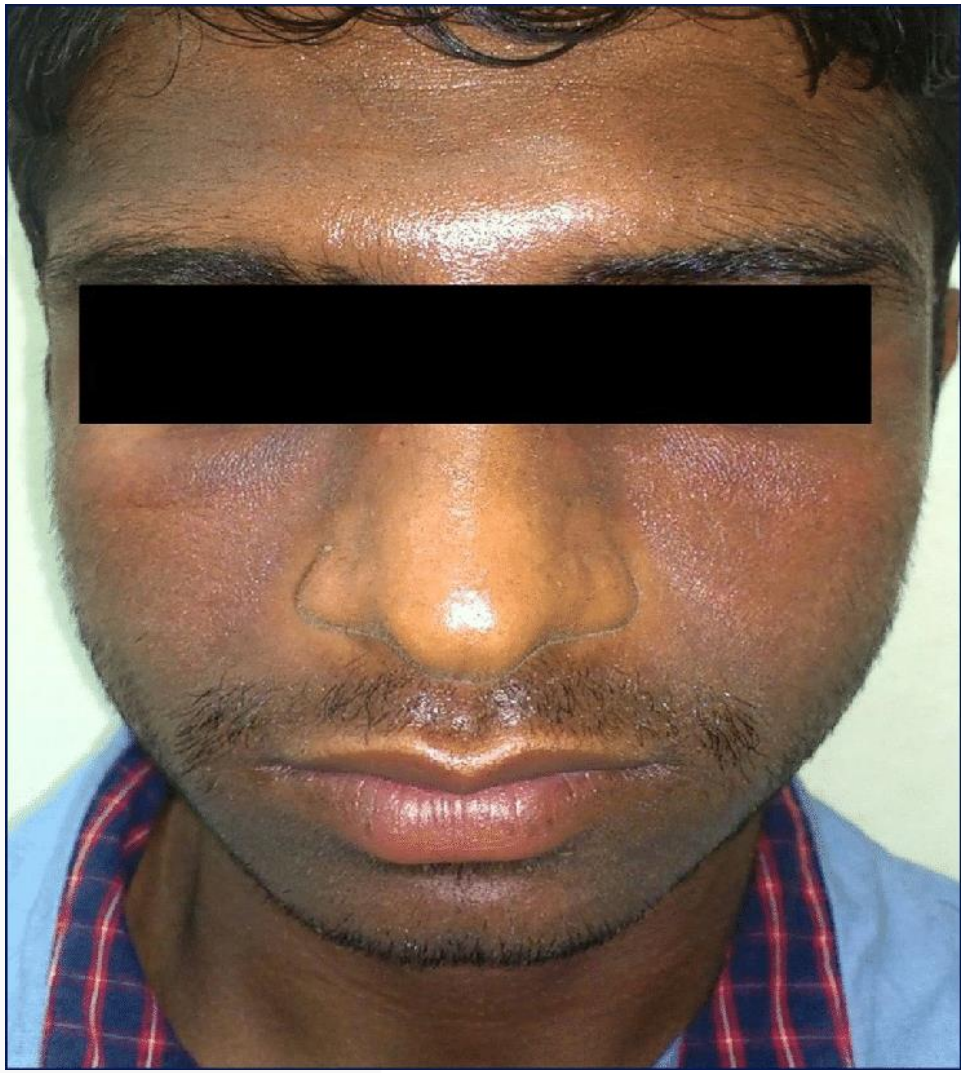
- Mustard oil (which contains allyl isothiocyanate, a potential photosensitizer) and amla oil have been suggested as possible inciting agents .
- There are multiple reports of the coexistence of LPP and frontal fibrosing alopecia, illustrating that LPP may be the herald sign of this scarring type of hair loss and that both entities may have a pathogenic link.

Lichen planus pigmentosus

Clinical features

- LPP typically presents with oval or irregularly shaped, brown to gray-brown macules and patches in sun-exposed areas, including the forehead, temples, and neck .
- It may also occur on the trunk and in intertriginous areas (lichen planus pigmentosus inversus).
- Lesions are usually symmetric but can present in a unilateral, linear fashion.
- In contrast with erythema dyschromicum perstans, early LPP lesions lack an erythematous border.

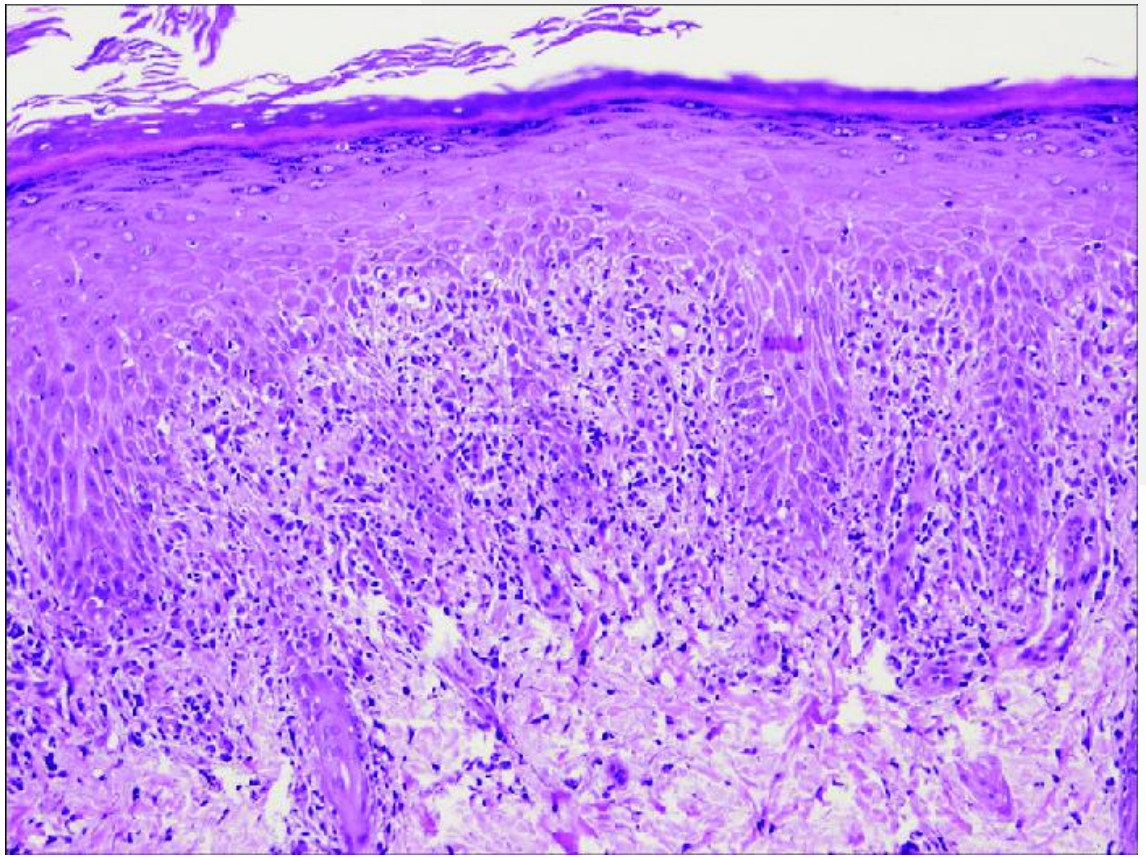
Lichen planus pigmentosus



Lichen planus pigmentosus

Histology:

- Hyperkeratosis
- Vacuolar cell degeneration in the basal layer with apoptotic keratinocytes
- A band-like dermal lymphocytic infiltrate with pigment incontinence, and melanophages.



Treatment of Lichen planus pigmentosus

- LPP is a chronic, relapsing disorder with exacerbations and remissions.
- First-line treatment involves the use of sun-protective measures to prevent further darkening.

Other treatment options include:

- Topical corticosteroids
- Topical calcineurin inhibitors
- Skin-lightening agents
- Oral retinoids
- UV light therapy
- Antimalarials
- Laser therapy

Drug-induced hyperpigmentation

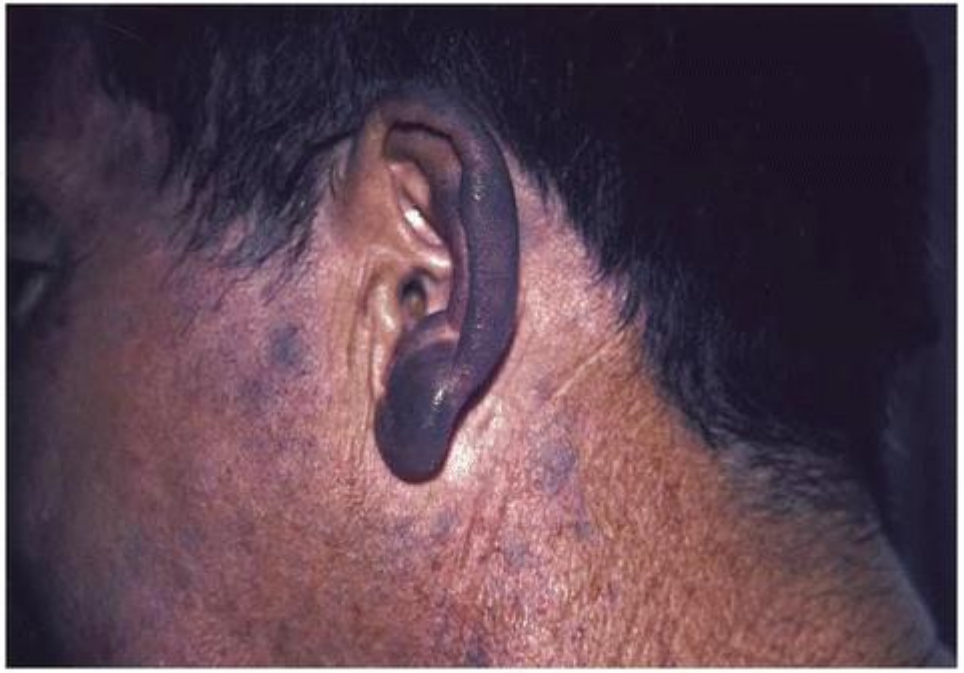
- Drug-induced hyperpigmentation accounts for 10–20% of all cases of acquired hyperpigmentation.
- Several mechanisms are involved in drug-induced changes of pigmentation of the skin:
  - Increased melanin synthesis
  - Increased lipofuscin synthesis
  - Deposition of drug-related material
  - Post-inflammatory hyperpigmentation

Drug-induced hyperpigmentation

- Amiodarone
- Antimalarials
- Clofazimine
- Minocycline
- Fixed drug eruption
- Ochronosis

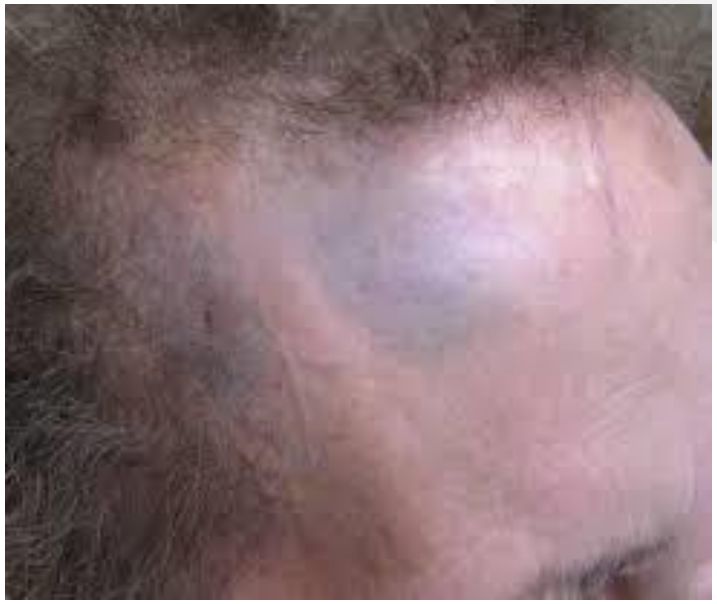
Amiodarone

- Fewer than 5% of patients develop drug-induced discoloration of the skin, characterized by a slate-gray or purple discoloration of mainly the sun-exposed skin,



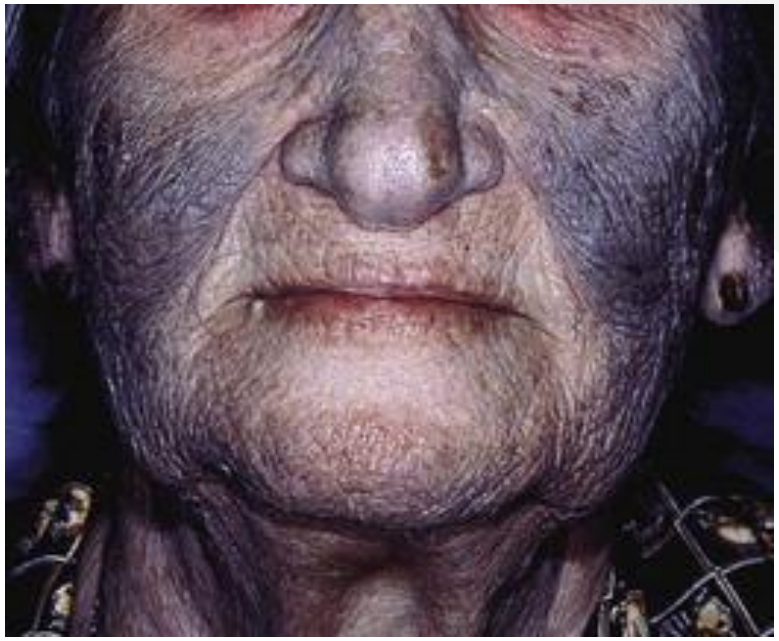
Antimalarial drugs

- Bluish-grey pigmentation appears mainly on sun-exposed areas.
- Bleaching of the color of the hair occurs.



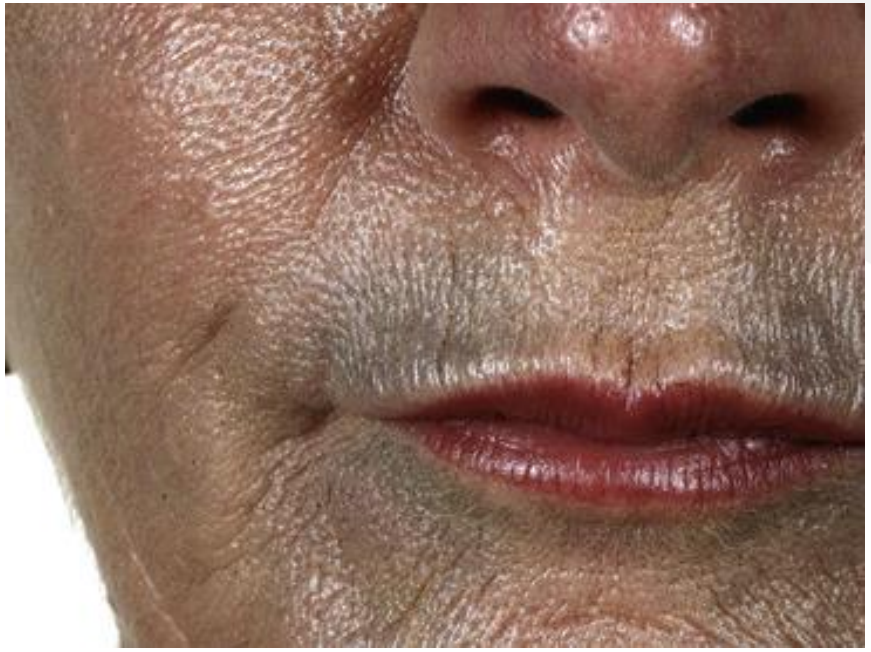
Clofazimin

- It produces an initial redness of the skin due to an accumulation of the drug.
- Later, with prolonged treatment, a violaceous brown colour develops that is most noticeable in face and lesional skin.



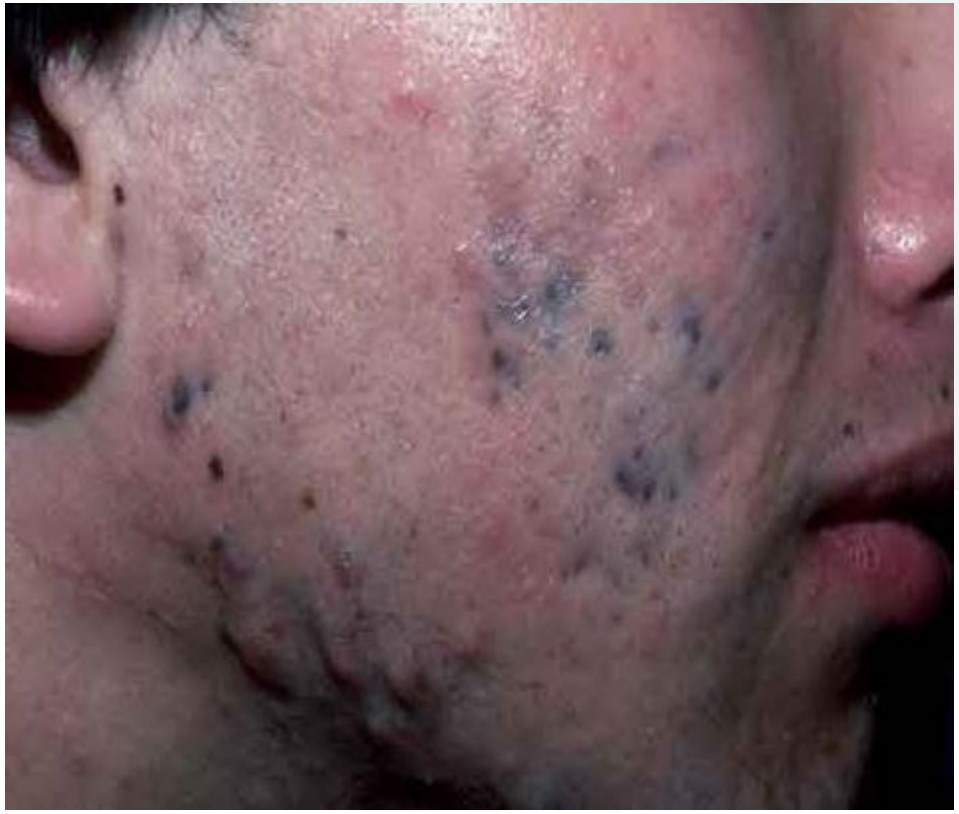
Minocyclin

- Minocycline-induced hyperpigmentation may affect up to 15% of patients receiving minocycline, particularly in long-duration treatments.



Minocyclin

- Four unique patterns with well-circumscribed blue-grey macules located:
  - In areas of acne scars (type I)
  - At sites of previous inflammation and mostly affecting sun-exposed areas (type II)
  - ‘Muddy skin syndrome’ characterized by diffuse symmetrical brown-grey discoloration with a tendency to photo-aggravation (type III)
  - The vermilion of the lower lip (type IV)

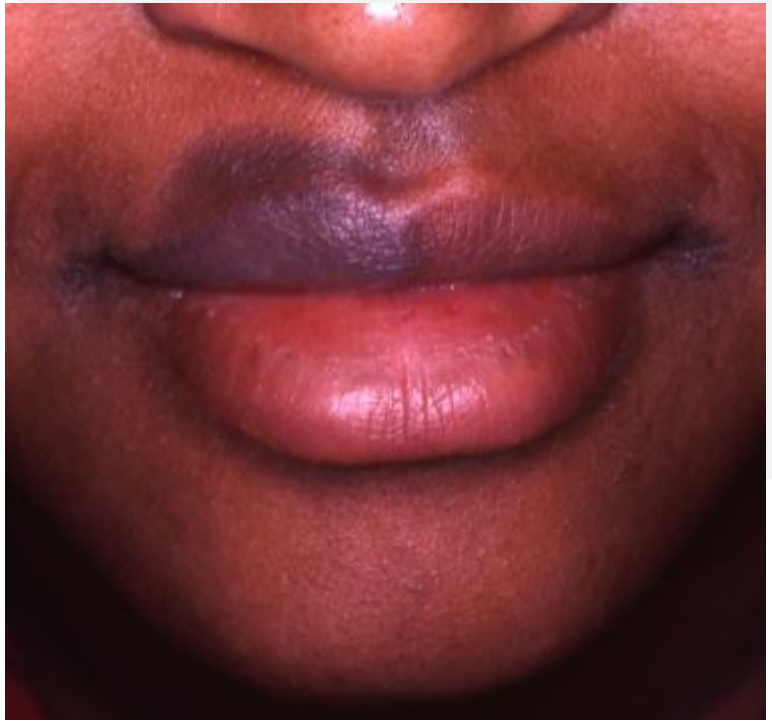


Fixed drug eruption

- Fixed drug eruption is one of the most common forms of drug-induced exanthems.
- The acute eruption characteristically settles leaving residual hyperpigmentation, especially in those with darker skin types so they are particularly frequent in black people.
- Most frequently reported drugs include tetracyclines, non-steroidal anti-inflammatory drugs, sulfonamides and sedatives.

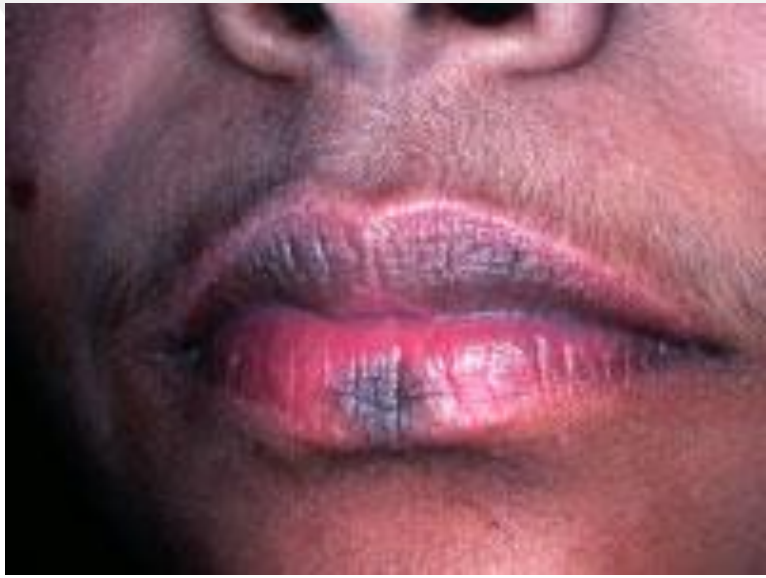
Fixed drug eruption

- Clinical features:
  - Well-circumscribed areas of slate-brown pigmentation commonly follow the erythematous and bullous stages of fixed eruptions .
  - The genitalia and perianal area are often affected, although the eruption can appear anywhere on the skin surface.



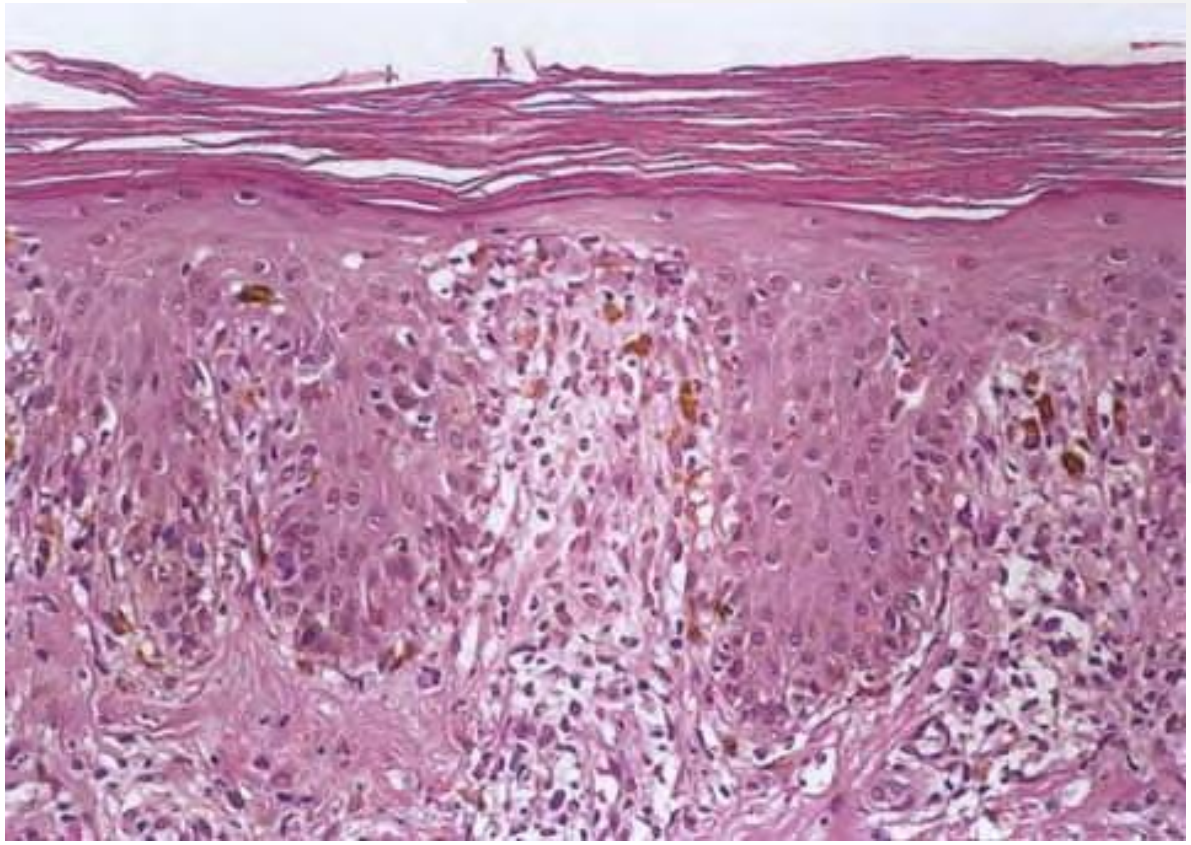
Fixed drug eruption

- Clinical features:
  - The characteristic course is recurrence of lesions at the same sites with development of new areas of involvement with repeated exposure to the causative agent.



Fixed drug eruption

- The slate-brown colour in fixed drug eruption is due to pigmentary incontinence with melanophages in the upper dermis .
- It is suggested that the eruption may be mediated by a type IV hypersensitivity.
- Immunohistological findings suggest that the characteristic same-site recurrence may be induced by prolonged ICAM-1 expression in the lesional keratinocytes.

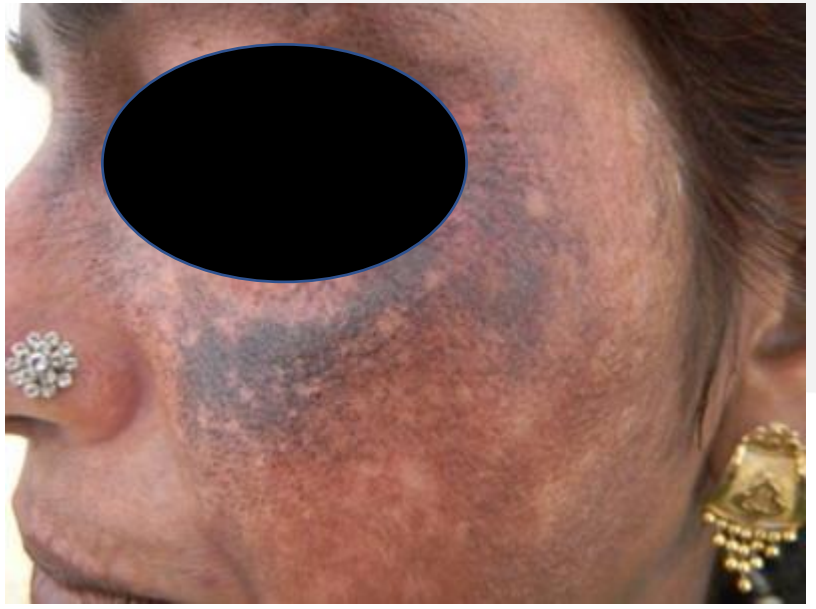


Ochronosis

- Ochronosis is the bluish black discoloration of certain tissues, such as the ear cartilage and the ocular tissue, seen with alkaptonuria, a metabolic disorder.
- Additionally, exogenous ochronosis can occasionally occur from exposure to various substances such as phenol, trinitrophenol, resorcinol, mercury, picric acid, benzene, hydroquinone, and antimalarials.

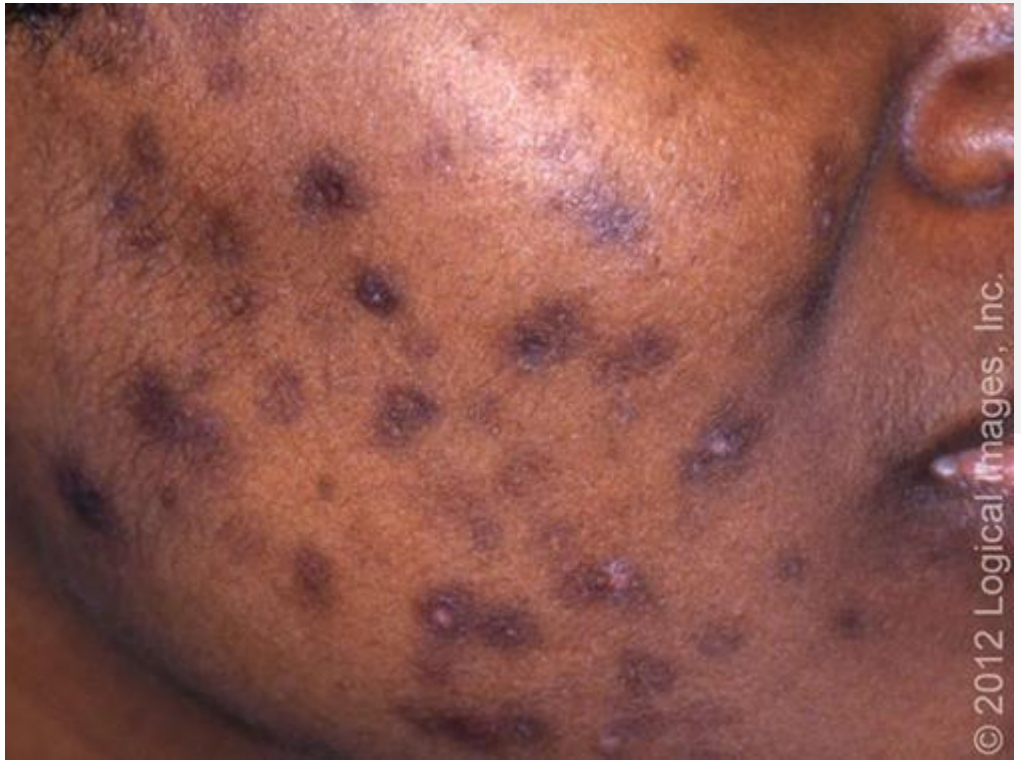
Ochronosis

- It is reported that 35% of African blacks exhibit ochronotic skin changes when using a 6-8% hydroquinone preparation over a prolonged period.
- This figure was 69% in a South African study.
- In African Americans, this cutaneous adverse effect of hydroquinones has been reported, even when using 2% hydroquinone products.
- With exogenous ochronosis, the arthropathy seen with alkaptonuria does not occur.



Postinflammatory hyperpigmentation (PIH)

- A reactive hypermelanosis of the skin that occurs as a sequela of cutaneous inflammation
- Common causes of PIH include acne vulgaris, eczematous dermatoses, and burn injury
- PIH is a frustrating problem that can have a strong psychologic toll on affected patients.



ETIOLOGY

Endogenous :

- Acne vulgaris, atopic dermatitis, irritant contact dermatitis, allergic contact dermatitis, psoriasis, and lichen planus

Exogenous:

- Accidental burns, nonionizing radiation therapy, phototoxicity, chemical peels, and laser procedures

PATHOGENESIS & HISTOPATHOLOGY

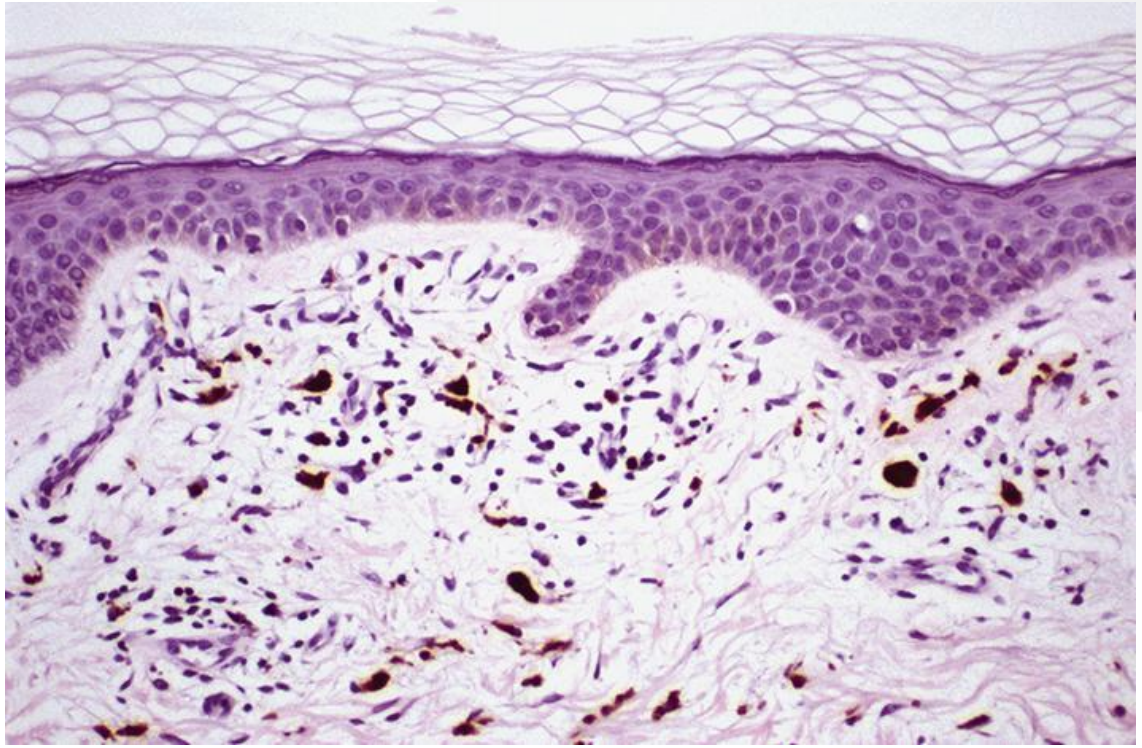
Epidermal Melanosis:

- Result from effects of the release and oxidation of arachidonic acid to prostaglandins and leukotrienes or the effects of other inflammatory mediators in inflamed skin
- Inflammatory mediators may stimulate melanocytes to increase production of melanin and transfer melanin to surrounding keratinocytes

PATHOGENESIS & HISTOPATHOLOGY

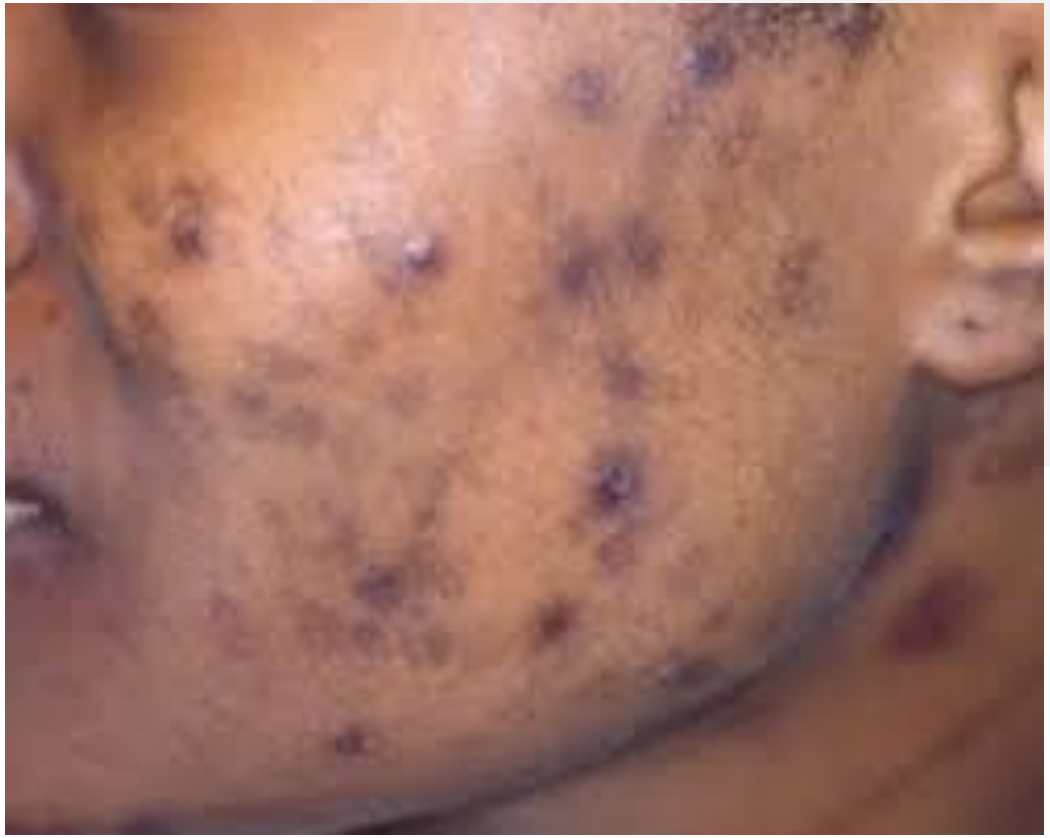
Dermal Melanosis:

- Pigmentary incontinence, may occur when inflammation leads to a disruption of the basal layer of the epidermis, causing the release of melanin into the papillary dermis
- Macrophages in the papillary dermis then phagocytize the released melanin
- Alternatively, macrophages may enter the epidermis, phagocytize epidermal melanosomes, and return to the dermis
- Macrophages that have phagocytized melanin are often called "melanophages



CLINICAL MANIFESTATIONS

- The color of PIH depends on the position of excess pigment within the skin.
- PIH tends to appear as tan to dark brown when excess pigment is within the epidermis.
- In contrast, excess pigment in the dermis tends to manifest with a dark gray or blue-gray appearance



TREATMENT

- A broad-spectrum sunscreen with SPF of at least 30
- Sun-protective clothing
- Elimination of exacerbating factors (acne, drug…)

First-line therapy:

- Topical hydroquinone

Second-line therapy:

- Topical retinoids
- Hydroquinone-retinoid-corticosteroid triple-agent therapy
- Azelaic acid
- Chemical peels
- Laser

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TEHRAN UNIVERSITY OF MEDICAL SCIENCES

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Medical treatment of melasma:
An evidence-based approach

Alireza Firooz, MD

Prof. of Dermatology and Director,
Center for Research & Training in Skin Diseases & Leprosy,And Clinical Trial Center,

Tehran University of Medical Sciences,
Tehran, Iran

Subtypes

- Depth:
  - Epidermal
  - Dermal
  - Mixed
- Vascular

- Thirty-six patients with melasma were recruited in this case-control study.
- Melanin index, erythema index, thickness of dermis and epidermis were significantly higher in melasma skin compasred to normal skin.
- Melasma subtype, age, skin type, location and duration of melasma had no significant effect on any of these variables.

Journal of Pigmentary Disorders

Rahrovan et al., Pigmentary Disorders 2015, 2:11
http://dx.doi.org/10.4172/2376-0427.1000222

Research Hybrid open access

Biophysical Characteristics of Melasma Skin Comparing with the Perilesional Normal Skin and its Relation to the Melasma Subtype

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Rec date: September 30, 2015; **Acc date:** November 02, 2015; **Pub date:** November 10, 2015

Abstract

Background: Melasma is a common disorder of hyperpigmentation affecting millions of people worldwide. All the exact pathways to understand the complete pathogenesis of melasma is unknown.

Aims: To determine the biophysical characteristics of melasma skin compared to the normal surrounding skin.

Methods: Thirty-six patients with melasma were recruited in this case-control study. The subtype of melasma (epidermal, dermal, or mixed) was determined by Wood lamp examination. The melanin index, erythema index, stratum corneum (SC), hydration, sebum content, transepidermal water loss (TEWL), temperature, friction index, and pH of lesional and perilesional normal skin of patients were measured in standardized temperature and humidity conditions. The epidermal and dermal thickness and dermal echo-density were determined on the same locations. The measurements were compared between lesional and perilesional normal skin using dependent t-test and among three subtypes of melasma using one-way ANOVA. P values of <0.05 were considered statistically significant.

Results: Melanin index, erythema index, SC hydration, pH, thickness of dermis and epidermis were significantly higher and the temperature was significantly lower in lesional skin compared with surrounding normal skin. No significant differences were found in TEWL, friction index, sebum content and density of dermis. Melasma subtype, age, skintype, location and duration of melasma had no significant effect on any of these variables.

Conclusions: Melasma skin is characterized by certain changes in biophysical factors of epidermis and dermis. The relation of these changes with the hyper-activity of melanocytes and melanin overproduction should be determined in future studies.

Vascular melasma

- Kim et al found that biopsy specimens of lesional melasma skin had greater VEGF expression in keratinocytes compared to nearby nonlesional skin.
- VEGF could have a direct influence on melanocyte behavior through its receptor on them.
- Factor VIII related antigen staining showed that melasma skin had more numerous and larger blood vessels compared to uninvolved skin.
- Sonthalia et al via dermatoscopic examination of melasma reported the existence of a vascular form of melasma with increased vascularity and evident telangiectasias different from the “nonvascular melasma type.”

Treatment

- Avoidance of trigger factors,
- Photoprotection,
- Topical depigmenting agents
  - HQ
  - Non-HQ
- Systemic treatment

Exacerbating factors

- Sun exposure
- Pregnancy
- OCP
- Thyroid disease

Photoprotection

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DOI: 10.1111/jocd.12911

ORIGINAL CONTRIBUTION

WILEY JCD Journal of Cosmetic Dermatology

Role of broad-spectrum sunscreen alone in the improvement of melasma area severity index (MASI) and Melasma Quality of Life Index in melasma

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Funding Information
The study was funded by a research grant provided by IADVL (Indian Association of Dermatologists, Venereologists and Leprologists)-L'Oreal Hair and Skin Research Grant.

Abstract

Background: Sunscreens have long been an indispensable part in treating melasma as ancillary agents. None of previous studies have evaluated the role of sunscreens alone in the improvement of melasma.

Aims: Our objective was to study the role of broad-spectrum sunscreen with sun protection factor 19 and PA+++ as the sole agent for improvement of melasma.

Methods: A total of 100 patients with melasma were included in the study. Following proper method of application of 3 mL sunscreen, thrice daily, Melasma Area Severity Score (MASI) and Hindi language version of the MELASQOL scale (Hi-MELAQOL) was done at baseline and 12 weeks.

Results: The mean MASI in the study group at the beginning and at the end of the study was 12.38 ± 14.7 and 9.15 ± 4.7, respectively, whereas the mean value of Hi-MELASQOL at the beginning and at the end of the study was 47.2 ± 14 and 38.1 ± 14.2, respectively. The differences of both were statistically significant. Spearman's correlation between MASI and Hi-MELASQOL before and after the study was positive but insignificant.

Conclusion: There was both an objective and subjective improvement in melasma after 12 weeks of sunscreen use in terms of both MASI, showing an objective improvement of melasma after using sunscreens alone and also in Hi-MELASQOL showing that use of sunscreens significantly improved quality of life of melasma patients. In our study, we have attempted to re-instate the importance of sunscreens to patients and dermatologists who are inclining more toward various skin lightening agents for treatment of melasma, which have many side effects.

KEYWORDS
melasma, quality of life, sunscreen

- A total of 100 patients with melasma were included in the study.
- Following proper method of application of 3 mL sunscreen, thrice daily, for 12 weeks.
- The mean MASI in the study group at the beginning and at the end of the study was 12.38 ± 14.7 and 9.15 ± 4.7, respectively.
- The mean value of Hi-MELASQOL at the beginning and at the end of the study was 47.2 ± 14 and 38.1 ± 14.2, respectively.

Topical treatment

Table I. Agents under investigation to decrease cutaneous hyperpigmentation

Proposed mechanism of action	Compound
Tyrosinase inhibition	Hydroquinone
	Mequinol
	Azelaic acid
	Arbutin and deoxyarbutin
	Licorice extract
	Rucinol
	Resveratrol
	4-hydroxy-anisole
	2,5-dimethyl-4-hydroxy-3(2*H*)-furanone
	N-acetyl glucosamine
Stimulation of keratinocyte turnover	Retinoids
Reduction in melanosome transfer	Retinoids, soybean trypsin inhibitor
Interaction with copper	Kojic acid
	Ascorbic acid
Inhibition of melanosome maturation	Arbutin and deoxyarbutin
Inhibition of protease-activated receptor 2	Soybean trypsin inhibitor
Inhibition of plasmin	Tranexamic acid
Reduction of alpha melanocyte-stimulating hormone–induced melanin production	Beta-carotene

Review article

CED
Clinical and Experimental Dermatology

CPD

Hydroquinone: myths and reality

T. Searle,[1] F. Al-Niaimi[2] and F. R. Ali[3,4]

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[3]*St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK; and* [4]*Vernova Healthcare CIC, Macclesfield, UK*

doi:10.1111/ced.14480

Table 1 Hydroquinone summary.

Uses	Melasma, chloasma, solar lentigines, freckles and postinflammatory hyperpigmentation
Recommended concentration	2%–5%
Recommended treatment period	3 months–1 year
KF	Hydroquinone 5%, tretinoin 0.1% and dexamethasone 0.1%
Modified KF	Hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01% (Tri-Luma Cream, Galderma, USA) Hydroquinone 5%, tretinoin 0.1%, hydrocortisone 1% (Pigmanorm® cream; Louis Widmer GmbH, Rheinfelden, Germany)
Possible AEs	Mild erythema, exogenous ochronosis

Hydroquinone

A New Formula for Depigmenting Human Skin

Albert M. Kligman, MD, PhD, Isaac Willis, MD

Complete depigmentation of the normal skin of adult male blacks was procured by the daily application for five to seven weeks of a formula consisting of 0.1% tretinoin, 5.0% hydroquinone, 0.1% dexamethasone, and hydrophilic ointment. Depigmentation was not attainable when any one of the components was omitted.

The formula was therapeutically effective in treatment of melasma, ephelides, and postinflammatory hyperpigmentation. Senile lentigines were resistant to this therapy.

Pigmentary changes are an important source of human misery. They immediately set one apart and consequently threaten psychosocial and psychosexual identity. Pigmentary nonconformists are never praised and are generally viewed as odd and unattractive. The lack of physical impairment is but slight compensation for the mental anguish of the outcast with too little or too much melanin, especially when the changes occur in bizarre patterns.

Physicians have lagged considerably behind laymen in appreciating that these afflictions merit medical attention; even today scientists of high ability and low sensitivity refer to pigmentary abnormalities as "cosmetic." One untoward effect of such cavalier "put-downs" is to divert individuals with pigmentary problems to beauticians rather than physicians. Dermatologists, happy to say, generally accord these patients the sympathy they need and are well schooled in the utilization of available remedies.

The current therapy for hyperpigmentation is unsatisfactory. Although a great deal is known about the biology and biochemistry of melanin synthesis, an acceptable means of reducing excessive melanization is not at hand.

HISTORICAL BACKGROUND

The ancients showed great enterprise in the search for agents that would lighten hyperpigmented skin. The fact that many of their methods are still with us today eloquently describes our therapeutic impotency. Heavy metals, especially salts of mercury, are still widely used often in combination with salicylic acid. They are partially but inconsistently effective. Enzyme inhibition is the probable mode of action. The possibility of systemic poisoning is a good reason why mercury should not be used day after day. Oxidizing agents, such as peroxides and chlorates, are more effective bleaches for hair than skin. Reducing agents, such as organic acids and lemon juice, aim to transform melanin to the colorless leukoform. These have marginal effects on the integument.

What might be called the modern period began when Oettel produced grey hair in black cats by feeding them hydroquinone.[1] Since that time the capacity of this agent to produce depigmentation has been demonstrated in fish, rodents, and man.[2,3,4]

An occupational accident in 1939 triggered a tremendous interest in the possible therapeutic applications of hydroquinone derivatives.[5] Black workers in a tannery experienced depigmentation of the hands under the area covered by rubber gloves. The responsible agent proved to be the anti-oxidant, monobenzylether of hydroquinone (MBEH). Lerner and Fitzpatrick then showed that this chemical could depigment the normal skin of blacks and was indeed useful for alleviating pathologic hyperpigmentation.[6] Creams containing up to 20% MBEH became available by prescription. Hope, however, soon gave way to uncertainty; doubt then developed into despair.

Becker and Spencers' study of MBEH doomed this agent.[7] They made daily applications in vanishing cream to the normal skin of blacks for four months. They could not procure a uniform, controllable depigmentation. Approximately 25% of the subjects showed no lightening when treated with drug concentrations ranging from 1% to 20%. More seriously, about half of those patients whose skin became depigmented showed an extension of the leukoderma beyond the area of application; this continued for many months after treatment stopped. The appearance

Accepted for publication June 27, 1974.

From the Department of Dermatology, University of Pennsylvania, School of Medicine, Philadelphia.

Reprint requests to the Department of Dermatology, Duhring Laboratories, Hospital of the University of Pennsylvania, Philadelphia, PA 19104 (Dr. Kligman).

- Hydroquinone 5.0%;
- Tretinoin 0.1%;
- Dexamethasone 0.1%.
- The vehicle was either hydrophilic ointment or a solution consisting of equal parts of ethanol and propylene glycol.
- The cream and solution were never more than 30 days old.
- The addition of anti-oxidants did not enhance activity.

HQ combination

- Effectiveness of this combination of agents:
  - Tretinoin prevents the oxidation of hydroquinone, increases keratinocyte turn over and improves epidermal penetration, reduces melanosome transfer.
  - Topical steroid component reduces irritation from the other two ingredients and decreases cellular metabolism, which inhibits melanin synthesis.

Triple combination

- The only preparation that approved by FDA is a triple combination cream (TriLuma; Galderma Pharmaceuticals) that was brought to market as an investigational drug approved by the FDA after the performance of adequate clinical trials.
- In the European Union, hydroquinone has been banned from use as a cosmetic ingredient since 2001 however, it is still available as a prescription medication in many countries.

Triple combination

- One of the most successful combination formulations has been :
  - 4% hydroquinone,
  - 0.05% tretinoin,
  - 0.01% fluocinolone acetonide.
- This triple combination was initially studied in a large number of melasma patients in a multicenter, investigator blinded, randomized prospective trials.
- 77% of patients on the triple-combination agent achieved complete or near-complete clearance.
- 48.8% had related adverse events but most were mild (erythema, irritation and discomfort) and none severe.
- Topical therapy with a triple combination agent appears to be the most clinically effective initial therapy for patients with melasma (J Am Acad Dermatol 2011;65:699-714).

Maintenance

- A suggested maintenance regimen comprises TCC applied twice weekly for 12 weeks.
- TCC maintenance therapy on a tapering regimen (three times weekly for the first month, twice weekly for the second month and once weekly for the fourth month) could prevent relapse in more than 50% of patients.

HQ TAM Formula
(J Cosmet Dermatol 2020 Nov 18)

- Patients and Methods: A pilot study of 6 women with melasma was conducted at an academic dermatology department and a private dermatology practice to evaluate the efficacy of a topical combination of 12% hydroquinone, 6% kojic acid, and 5% vitamin C cream, entitled the “Tam Formula” for at least 4 weeks.
- Two blinded evaluators calculated Melasma Area and Severity Index (MASI) Scores before and after treatment to evaluate change from baseline, and statistical analysis was performed.
- Results: Treatment with this combination topical cream resulted in an average 63.77 ± 22.10 percent reduction in MASI Scores.

HQ safety

- Hydroquinone is a compound that is commonly found in many foods and beverages, including berries, tea, coffee, red wine, wheat, and the skin of pears.
- Workers involved in the manufacture of hydroquinone and who are exposed to large quantities of this agent have not been found to have any significantly increased risk of premature death or increased prevalence of malignancy compared to controls.
- Hydroquinone has not been found to be carcinogenic in the Ames test.
- In addition, oral and systemic injections of hydroquinone in animals did not lead to the formation of malignancies or cause marrow toxicity.

Side effects

- Although oral hydroquinone is associated with cancer in animal studies, there have been no cases of human carcinogenicity reported.
- Exogenous ochronosis included patients who had used high concentrations of hydroquinone on large areas of skin, numerous times a day for years.
- Across 72 studies with 20 814 patients using 2%–5% hydroquinone over periods ranging from 8 weeks to 2 years, there were no reports of ochronosis when hydroquinone was prescribed and used under close medical supervision

Topical Non-HQ

- Ascorbic acid
- Retinoids
- Mequinol
- Azelaic acid
- Kojic acid
- Arbutin/deoxyarbutin
- Licorice extract
- Soy
- Rucinol
- Tranexamic acid
- Cysteamine
- Glutathione
- Methimazole

International Journal of Dermatology

Pharmacology And Therapeutics

A comparative study of topical 5% cysteamine versus 4% hydroquinone in the treatment of facial melasma in women

Paula Basso Lima[1], MD, Joana Alexandria Ferreira Dias[1], MD, Daniel Cassiano[2], MD, Ana Cláudia Cavalcante Esposito[1], MD, MSc, Ediléia Bagatin[2], MD, PhD, Luciane Donida Bartoli Miot[1], MD, PhD and Hélio Amante Miot[1], MD, PhD

Methods:

- 40 women with facial melasma who were submitted to the nightly application of 5% cysteamine (CYS) or 4% hydroquinone (HQ) on hyperpigmented areas for 120 days.
- Both groups were required to use tinted sunscreen (SPF 50; PPD 19).
- Subjects were assessed at the inclusion and after 60 and 120 days of treatment for mMASI, MELASQoL, and the difference in colorimetric luminosity between melasma and the adjacent unaffected skin.

Results:

- The mean reduction of the mMASI scores was 24% for CYS and 41% for HQ (P = 0.015) at 60 days, and 38% for CYS and 53% for HQ (P = 0.017) at 120 days.
- The photographic evaluation revealed up to 74% improvement for both groups, without statistically significant difference between them (P = 0.087).
- The MELASQoL score showed a progressive decrease for both groups over time, despite the greater reduction for HQ after 120 days (P = 0.018).
- Erythema and burning were the most important local adverse effects with cysteamine, although their frequency did not differ between groups (P > 0.170)

Australasian Journal of Dermatology

Australasian Journal of Dermatology (2020) ••, ••–••

doi: 10.1111/ajd.13432

ORIGINAL RESEARCH

Evaluation of the efficacy of cysteamine cream compared to hydroquinone in the treatment of melasma: A randomised, double-blinded trial

Jennifer Nguyen[1] | Laura Remyn[2] | In Young Chung[3] | Anthony Honigman[4] | Shima Gourani-Tehrani[5] | Ilycia Wutami[2] | Celestine Wong[5,6] | Eldho Paul[7] | Michelle Rodrigues[5,8]

- A randomised, double-blinded, singlecentre trial was conducted in 20 recruited participants were given either cysteamine cream 5% washed off after 15 min or hydroquinone 4% cream for 16 weeks.
- Results: At week 16, 14 participants completed the study with 5 participants in the cysteamine group and 9 patients in the hydroquinone group.
- There was 21.3% reduction in mMASI for the cysteamine and 32% reduction in the hydroquinone group. (P = 0.3)
- Hydroquinone cream was generally better tolerated that cysteamine cream.

Oral

- Tranexamic acid,
- Carotenoids,
- Glutathione,
- Melatonin,
- Polypodium leucotomos hydrophilic extract,
- Procyanidin

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DOI: 10.1111/jocd.12747

REVIEW ARTICLE

WILEY JCD Journal of Cosmetic Dermatology

The role of systemic treatments for skin lightening

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Summary

Background: Pigmentation of the skin occurs as a result of increased melanin production or deposition due to various reasons including age, hormonal imbalances, endocrine disease, inflammation, and/or exposure to damaging radiation, resulting in dermatologic conditions such as lentigines, melasma, or postinflammatory hyperpigmentation. Although numerous topical therapies exist for skin lightening, they are limited by efficacy and pigmentation recurrence after treatment cessation. New research into systemic therapies for hyperpigmentation has been promising.

Objective: To summarize the current literature for systemic skin lightening therapies.

Methods: A review of the literature surrounding systemic skin lightening therapies was completed using PubMed (US National Library of Medicine).

Results: Multiple systemic therapies for skin lightening exist including oral carotenoids, glutathione, melatonin, *Polypodium leucotomos* hydrophilic extract, procyanidin, and tranexamic acid. Preliminary data for the treatment of hyperpigmentation are promising, and currently, these oral treatments appear safe. It is not suggested to use intravenous glutathione for skin lightening due to the increased risk of adverse events.

Conclusion: With the patient population seeking effective systemic treatments for skin pigmentation, it is important for dermatologists to understand the properties, the efficacy, and the adverse events profile of each compound, thus ensuring proper use by patients, and that patients are appropriately counseled regarding treatment expectation and safety.

KEYWORDS

hyperpigmentation, lentigines, melasma, skin brightening, skin lightening, systemic therapy

- Preliminary data for the treatment of hyperpigmentation are promising, and currently, these oral treatments appear safe.
- It is not suggested to use intravenous glutathione for skin lightening due to the increased risk of adverse events.

Oral Tranexamic acid

ActaDV Acta Dermato-Venereologica ActaDV Advances in dermatology and venereology

SPECIAL REPORT

Check for updates

1

Efficacy and Safety of Tranexamic Acid in Melasma: A Meta-analysis and Systematic Review

Hyun Jung KIM[1*], Seok Hoon MOON[2*], Sang Hyun CHO[2], Jeong Deuk LEE[2] and Hei Sung KIM[2]

[1]Department of Preventive Medicine, Korea University College of Medicine, Seoul, and [2]Department of Dermatology, Incheon St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

*These authors contributed equally to this work.

Tranexamic acid is a novel treatment option for melasma; however, there is no consensus on its use. This systematic review searched major databases for relevant publications to March 2016. Eleven studies with 667 participants were included. Pooled data from tranexamic acid-only observational studies with pre- and post-treatment Melasma Area and Severity Index (MASI) showed a decrease of 1.60 in MASI (95% confidence interval (CI), 1.20–2.00; $p < 0.001$) after treatment with tranexamic acid. The addition of tranexamic acid to routine treatment modalities resulted in a further decrease in MASI of 0.94 (95% CI 0.10–1.79; $p = 0.03$). Side-effects were minor, with a few cases reporting hypomenorrhoea, mild abdominal discomfort, and transient skin irritation. These results support the efficacy and safety of tranexamic acid, either alone or as an adjuvant to routine treatment modalities for melasma.

Key words: tranexamic acid; melasma: systematic review; meta-analysis.

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Melasma is a common acquired disorder of facial pigmentation with predominance in the Asian population. Various treatment modalities have been used, but with inconsistent results (1, 2). Topical bleaching agents are the mainstay of treatment, but are often insufficient. Intense pulsed light (IPL) or laser-based treatments have conflicting outcomes with significant side-effects, such as mottled hypopigmentation and paradoxical darkening of melasma (3).

Increased pigmentation is the main feature of melasma. Although the exact pathogenesis is unknown, it has been hypothesized that melasma is induced by biologically active melanocytes (4). Increased vascularity in the affected skin and elevated expression of angiogenic factors in the epidermis have been found. These factors may play an important role in the development of melasma (4–6).

Tranexamic acid (TA), a synthetic derivative of lysine, is a well-known haemostatic agent. TA is anti-fibrinolytic. It can inhibit plasminogen activation through the reversible blockade of lysine-binding sites on plasminogen molecules (7).

In recent years, off-label TA has emerged as potential treatment for melasma (5, 8). Although the mechanism of action remains unclear, it is thought that TA may inhibit melanin synthesis by blocking the interaction between melanocytes and keratinocytes. TA may also reverse the abnormal dermal changes associated with melasma, such as the aforementioned increased vasculature (9).

While different forms of TA (i.e. oral, topical and localized microinjections) have shown promising results (7, 9–11), there is a lack of support for its efficacy and safety in melasma due to the absence of sufficiently powered randomized controlled trials (RCTs). Through a systematic review of the literature, we aimed to investigate the effectiveness and safety of TA, alone, or as an adjuvant, in patients with melasma.

MATERIALS AND METHODS

A systematic review and meta-analysis were conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement (12).

Search strategy

A systematic review of studies of the effect of TA in melasma was carried out. In order to collect all available evidence, EMBASE (1988 to present), MEDLINE (1946 to present), Web of Science (1975 to present), Scopus (1996 to present), and the Cochrane Central register of Controlled Trials (CENTRAL) (1991 to present) databases were searched on 4 March 2016, without limitation as to dates or language. To search for studies of TA, the following keywords were used: "tranexamic acid', "antifibrinolytic agents" and 'tranexamic". To search for melasma, the following keywords were used: "melanosis", "chloasma", "chloasmas", "melasma", and "melasmas". The full search strategy, shown in Appendix S1[1], was developed for MEDLINE and tailored to the other electronic databases.

Study selection

Inclusion criteria were: original reports (study, case series, item of correspondence, posters and meeting abstracts) describing treatment with any form of TA, alone or as an adjunct in melasma (human). According to the pre-defined criteria, 2 authors (H.J.K. and H.S.K.) independently selected reports based on the title and abstracts. Any discrepancies were resolved in consultation with a

[1]https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-2668

doi: 10.2340/00015555-2668
Acta Derm Venereol 2017 Epub ahead of print

- Eleven studies with 667 participants were included.
- Pooled data from tranexamic acid-only observational studies with pre and post-treatment Melasma Area and Severity Index (MASI) showed a decrease of 1.60 in MASI (95% confidence interval (CI), 1.20–2.00; p < 0.001) after treatment with tranexamic acid.
- The addition of tranexamic acid to routine treatment modalities resulted in a further decrease in MASI of 0.94 (95% CI 0.10–1.79; p = 0.03).
- Side-effects were minor, with a few cases reporting hypomenorrhoea, mild abdominal discomfort, and transient skin irritation.

Interventions for melasma (Review)

Rajaratnam R, Halpern J, Salim A, Emmett C

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 7

http://www.thecochranelibrary.com

WILEY

Systematic review of randomized controlled trials on interventions for melasma: An abridged Cochrane review

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Birmingham, Walsall, Chester, and Stoke on Trent, United Kingdom

See related articles on pages 281 and 352

Background: Multiple treatments exist for melasma; they are often substandard and associated with side effects.

Objectives: We sought to assess the effectiveness of interventions used in the management of all types of melasma.

Methods: We undertook a systematic review using the methodology of the Cochrane Collaboration.

Results: We included 20 studies with a total of 2125 participants covering 23 different treatments. A meta-analysis was not possible because of the heterogeneity of treatments. Triple-combination cream (hydroquinone, tretinoin, and fluocinolone acetonide) was more effective at lightening melasma than hydroquinone alone (relative risk 1.58, 95% confidence interval 1.26-1.97) or any of the agents in a dual-combination cream. Azelaic acid (20%) was significantly more effective than 2% hydroquinone (relative risk 1.25, 95% confidence interval 1.06-1.48) at lightening melasma. In 2 studies where tretinoin was compared with placebo, objective measures demonstrated significant reductions in the severity. However, only in 1 study did participants rate a significant improvement (relative risk 13, 95% confidence interval 1.88-89.74).

Limitations: There was poor methodology, a lack of standardized outcome assessments, and short duration of studies.

Conclusions: The current limited evidence supports the efficacy of multiple interventions. Randomized controlled trials on well-defined participants with long-term outcomes are needed. (J Am Acad Dermatol 2014;70:369-73.)

Key words: ascorbic acid; azelaic acid; chloasma; glycolic acid; hydroquinone; melasma; pigment; tretinoin; triple combination; vitamin C.

Treatments for melasma can be broadly classified into topical preparations, laser, or other therapies. Outcomes are variable and may be associated with side effects such as irritation and scarring.

The objectives of this study were to assess the effectiveness of interventions to treat melasma and avoid recurrence; investigate whether factors such as race, sex, and skin color had effect on treatment response; determine the incidence of

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The Cochrane Review is published with the support of the CRG.
Conflicts of interest: None declared.
This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2010, Issue 7, DOI:10.1002/1465 1858.CD003583 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.
Accepted for publication July 28, 2013.
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0190-9622/536.00

http://dx.doi.org/10.1016/j.jaad.2013.07.044

Cochrane review

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- In 2 studies where tretinoin was compared with placebo, objective measures demonstrated significant reductions in the severity.

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ORIGINAL CONTRIBUTION

JCD Journal of Cosmetic Dermatology WILEY

Melasma: A critical analysis of clinical trials investigating treatment modalities published in the past 10 years

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Abstract

Background: Melasma is an acquired disorder of facial pigmentation which is a treatment challenge.

Aims: The aim of this article is to critically appraise the clinical trial evidence for different treatment modalities for melasma, published in peer-reviewed journals in the past 10 years.

Patients/Methods: The literature review was conducted using PubMed and MEDLINE. The search was performed in July 2019, and search parameters were limited to all English language articles published in the past 10 years only.

Results: Eighty-nine clinical trials were found. Four clinical trials investigated topical hydroquinone, supporting its safety and efficacy as first-line treatment. Twelve studies showed tranexamic acid as very promising. Nineteen studies assessed various novel oral, injectable, and topical treatments and highlight some new potential future treatments. Forty-two studies investigated laser and light treatment in melasma: LFQS laser is still one of the best options, especially in darker skin types. However, the picosecond laser has shown excellent results. Finally, 11 studies looked at peels. Overall, peels have not been shown to be superior to the use of topical therapy alone.

Conclusion: Topical therapy with a HQ and retinoid-based product should be first line for a minimum of 3 months with the addition of oral tranexamic acid at 250 mg BD if no contraindication. Second-line treatment with lasers includes the LFQS Nd:YAG, picosecond laser, and the pulsed dye laser in lighter skin types. Third-line therapy would be the addition of chemical peels to the above treatments, with GA or TCA peels having the most evidence for effectiveness.

KEYWORDS
hydroquinone, melasma, pigmentation, tranexamic acid, tretinoin

1 | INTRODUCTION

Melasma is a common, acquired disorder of facial pigmentation which poses one of the greatest treatment challenges to the dermatologist and the aesthetic practitioner. Clinically, it is characterized by irregular brown macules and patches on the face.[1]

The exact cause is unknown but risk factors for melasma are well-established and include a history of sun exposure as well as exposure to visible light, Fitzpatrick skin types greater than III, pregnancy, the use of exogenous hormones such as the oral contraceptive pill and hormone replacement therapy, as well as a family history.[2] There is also emerging evidence for a significant vascular component in

- Eighty-nine clinical trials were found.
- Topical therapy with a HQ and retinoid-based product should be first line for a minimum of 3 months with the addition of oral tranexamic acid at 250 mg BD if no contraindication.
- Second-line treatment with lasers includes the LFQS Nd:YAG, picosecond laser, and the pulsed dye laser in lighter skin types.
- Third-line therapy would be the addition of chemical peels to the above treatments, with GA or TCA peels having the most evidence for effectiveness.

My practice

Is the diagnosis melasma?

Aggravating factors

-UV + visible light

- Hormonal

Treatment

Recurrence

Confirm the diagnosis

- History
- Physical examination
- Wood lamp exam
- Dermoscopy
- Biopsy

Avoid exacerbating factors

- Broad spectrum sunscreen with SPF at least 30
- Other sun protection measures
- Avoid irritation

Treatment

- First line:
- Triple combination (8-12 weeks): begin with small amount, short duration, long intervals, moisturizers
  - Good response: maintenance 1-2/wk, add non-HQ topical
  - Poor response: Add oral tranexamic acid (500-750 mg daily) if no contraindications
- Second line:
  - Non-HQ topical,
  - Microdermabrasion
  - Light sources: fractional QS Nd:YAG, picosecond laser, vascular laser, IPL
  - Chemical peeling: GA, TCA

Maintenance

- Sunscreens
- HQ weekly
- Topical non-HQ
- Fractional QS Nd:YAG every 2-3 months

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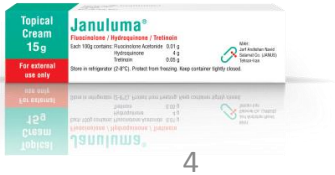
Nonpharmacologic Management of Melasma

Mehran Heydari Seradj, MD

Dermatologist

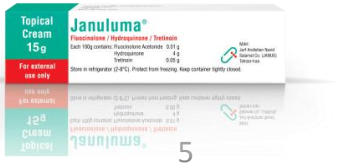
INTRODUCTION

- The management of melasma is often challenging, with incomplete responses in many cases and frequent relapses.
- A combination of therapies targeting multiple pathogenic elements, such as photodamage, inflammation, aberrant vascularity, and abnormal pigmentation, generally provides the best clinical outcomes.



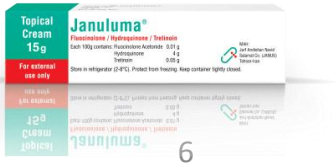
PRETREATMENT EVALUATION

- Pretreatment evaluation of the patient includes:
  - Assessment of severity and duration of melasma,
  - Specific risk and trigger factors,
  - Level of adherence to treatment, and
  - Willingness to adopt strict photoprotection measures.
- Use and response to previous treatments should also be assessed.
- As melasma is often influenced or triggered by hormone therapies, clinicians should personalize recommendations regarding the use of hormones, based on the unique needs of each patient.



PATIENT EDUCATION

- Patient education has a key role in the management of melasma.
- Clinicians should educate patients about the risk factors and triggers for melasma.
- The importance of daily use of a broadband sunscreen that protects against ultraviolet, visible, and even infrared light.
- The importance of consistent use of maintenance therapy to minimize the risk of recurrence.



APPROACH TO TREATMENT

- There is no standard therapy for melasma.
- In most cases, a multimodality approach is required, incorporating:
  - Photoprotection,
  - Skin lighteners,
  - Exfoliants, antioxidants, and
  - Resurfacing procedures, based on the patient's characteristics and clinical presentation.

Photoprotection

- Strict photoprotection, including sun avoidance, sun-protective clothing, and broad-spectrum sunscreens, is an essential component of all treatment and prevention regimens for melasma.
- We suggest daily use of a broad-spectrum sunscreen with a sun protection factor (SPF) of 50 or higher.
- Sunscreen should be applied in an adequate amount in the morning and reapplied every two to three hours while outdoors.
- While studies document the role of visible light in darker-skinned patients with melasma, there is a paucity of effective sunscreens blocking visible light.
- Chemical and mineral (zinc oxide and titanium dioxide-based) broad-spectrum sunscreens do not provide optimal protection from visible light.
- The most efficacious visible light sunscreens contain iron oxide in concentrations above 3%.
- Of note, iron oxide is the major pigment used in colored topical products and cosmetics.

Cosmetic camouflage

- Cosmetic camouflage is a technique that uses makeup to conceal skin lesions and normalize the appearance of the skin.
- It can mitigate the psychosocial impact of melasma and improve the patient's quality of life.
- Anhydrous (water-proof) foundations that contain titanium dioxide, zinc oxide, and iron oxide provide a dual benefit, as they act as cosmetic concealers and sunscreen. Cosmetic camouflage can be used during active treatment.

Treatment of Melasma

- **First-line therapies**
  - Topical skin-lightening agents
- **Second-line therapies**
  - **Chemical peels**
  - Oral tranexamic acid
- **Third-line therapies**
  - **Lasers and light therapies**

CHEMICAL PEELS

Chemical peeling involves the topical application of a wounding agent, wherein the desired outcome is a controlled regeneration of the skin, depending on the depth of penetration of the specific agent used

Types of chemical peels

- These agents remove definite skin layers which triggers epidermal regeneration, and are thus classified according to the histologic depth of peeling into:
  - Superficial very light,
  - Superficial light,
  - Medium-depth, and
  - Deep peels.
- The majority of clinicians using chemical peels for melasma utilize superficial or medium-depth peels.
- These include glycolic acid, other alpha-hydroxy acids, salicylic acid, Jessner's solution, and trichloroacetic acid.

Efficacy

- Glycolic acid is the most extensively studied peeling agent for melasma.
- In a review of studies assessing the efficacy of chemical peels, including glycolic acid, lactic acid, Jessner's solution, tretinoin, and salicylic acid, for the treatment of melasma in dark-skinned patients, glycolic acid peeling was associated with a moderate response in approximately one-half of the patients, with patients having the epidermal form of melasma showing the best response.

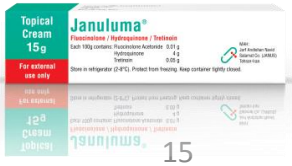
Adverse effects

- Possible adverse effects of chemical peels include infection, scarring (although this is rare during superficial peels), allergic reactions, milia, acneiform eruptions, persistent erythema (more than three weeks), and pigmentary changes.
- Due to the risk of pigmentation and scarring, deep and medium-depth chemical peels should be used with caution in patients with darker skin tones.

LASERS AND LIGHT THERAPIES

Lasers and light therapies are third-line therapies for melasma, appropriate for patients in whom topical treatments and often chemical peels have failed to produce adequate improvement.

Importantly, lasers and light sources should be used with great care and caution in darker-skinned individuals due to the risk of postinflammatory hyperpigmentation.



Introduction

- Patients should be informed that lasers and light therapies are not cures for melasma.
- Approximately one-half of patients experience a recurrence within three to six months of the end of treatment, irrespective of the device used.
- Recurrence may be associated with more intense pigmentation, which may be recalcitrant to subsequent treatment.
- Thus, clinicians should counsel patients about the importance of adhering to a maintenance regimen to minimize the risk of recurrence following laser or light therapy.

Quality-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG)

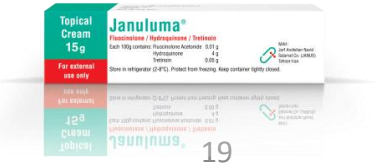
- The QS-Nd:YAG laser is the most commonly used laser for melasma, despite a relatively rapid relapse rate.
- QS-Nd:YAG lasers use a wavelength of 1064 nm, which is better absorbed by melanin than other skin structures.
- The QS-Nd:YAG laser also damages the upper dermal vascular plexus, which is abnormal in melasma, and promotes collagen formation in the surrounding dermis.

Pulsed dye laser (PDL)

- Angiogenesis contributes to melasma pathogenesis.
- The PDL is the gold standard for vascular lesions and, therefore, can target the vascular component of melasma.

Intense pulsed light (IPL)

- IPL delivers a broad spectrum of noncoherent light with a range of 500 to 1200 nm.
- The clinician can modulate various parameters, such as wavelength and the number, duration, and delay of pulses, allowing for more accurate targeting of the chromophore.
- Absorption of light by melanin results in thermolysis. This forms melanin-containing "crusts" that migrate to the cornified layer of the epidermis, from where they are shed.
- One study reported excellent results (80 to 100 percent reduction in hyperpigmented areas and dark tones) with IPL in 47 percent of 38 patients, good results (60 to 79 percent) in 29 percent, and moderate results (40 to 59 percent) in 13 percent.
- IPL targets all pigment in the skin and, therefore, may damage perilesional normal skin. IPL is thus not recommended in patients with darker skin tones (Fitzpatrick skin types IV through VI).



Efficacy

- 22 Asians, 5 wkly Rx with a QS-Nd:YAG + 2% HQ or 2% HQ alone. On laser side 93% improvement in lightness and 76% MASI score compared with 20 and 24 percent, respectively, on the control side.
- 40 Korean patients received 10 wkly Rx with a QS-Nd:YAG, MASI ↓ 54% at 10 wks.

Efficacy

- Microdermabrasion+QS-Nd:YAG+HQ+SS in 27 women with refractory melasma. Patients≈2.6 Rx at 4-week intervals. Most showed >50% clearance within a month of their first Rx. At 3 to 12 months after the end of treatment, 81% of the patients showed >75% and 40% showed more than 95% clearance.

Adverse effects

- Worsening of hyperpigmentation or mottled hypopigmentation may occur as a result of laser therapy.
- Patients should be instructed to adopt rigorous sun-protective measures after treatment, including sun avoidance and daily use of sunscreen.

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Side effects of lightening agents

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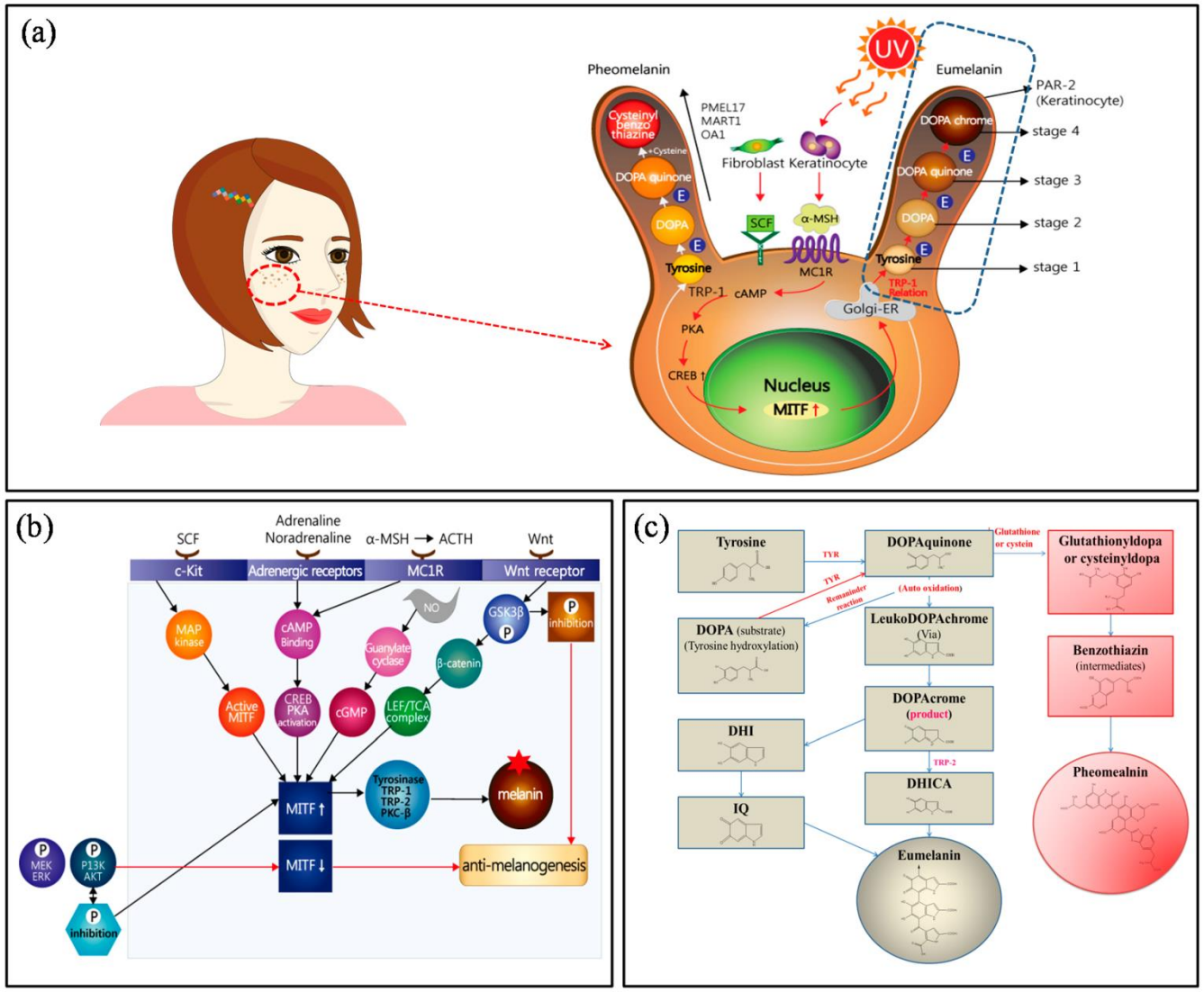
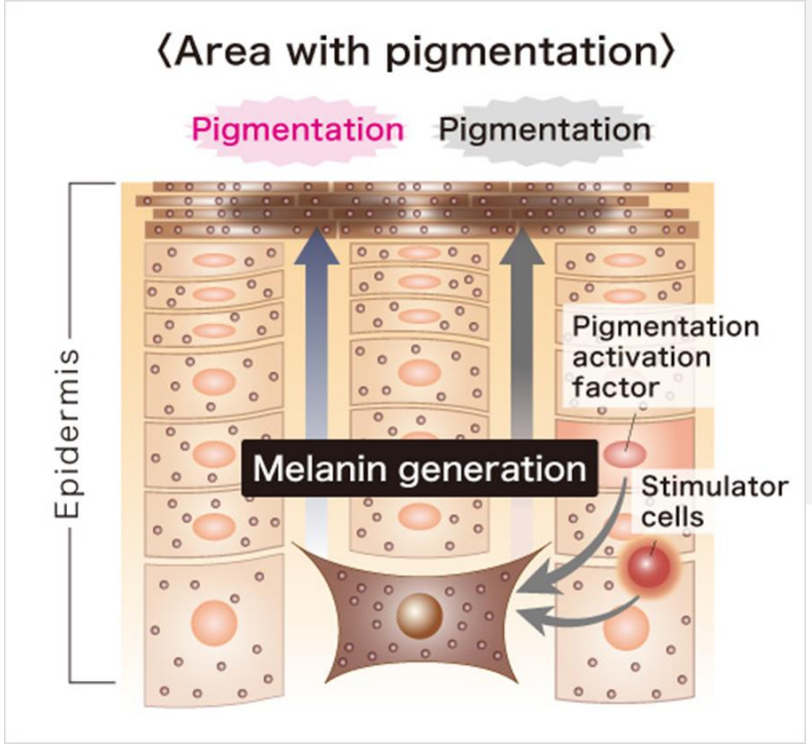
Introduction





Ultraviolet radiation

Visible light

Sun exposure
- ↑ Melanocyte proliferation
- ↑ Melanogenesis
- ↑ Dermal inflammation
- ↑ Fibroblast activation
- ↑ Stem cell factor
- ↑ Prostaglandin synthesis
- ↑ Inducible nitric oxide synthesis

Genetics and racial factors
- ↑ Predisposition in Fitzpatrick skin types III and IV
- Familiality in certain racial groups

Epidermal hypermelanoses
± Melanocytosis
± Dermal melanophages

Hormonal factors
- Onset and/or worsening during pregnancy
- ↑ Levels of sex hormones — controversial
- Hormone receptors — ? Dysregulated responses
- Oral contraceptive pills — ↑ risk of melasma

Vascular factors
- ↑ Number and size of blood vessels in lesional skin
- ↑ Expression of VEGF, b-FGF, IL-8 in lesional skin
- ↑ Release of mediators — arachidonic acid derivatives and plasminogen

- During the last few years, **a number of topical therapies**, including combination regimens, have become available for the treatment of hyperpigmentation.

- Most of these agents attempt to decrease pigmentation by interfering with various steps of the **melaninogenesis process** → **tyrosinase** as a key component in this process → the major target for many of the agents

- First and foremost, it is essential to identify and treat any **underlying dermatoses** → can cause postinflammatory hyperpigmentation **(PIH).**

- emphasis on **sun protection** and physical barriers

- **Chemical sunscreens** → can rarely cause an allergic or irritant contact dermatitis in patients with skin of color → PIH →→ caution

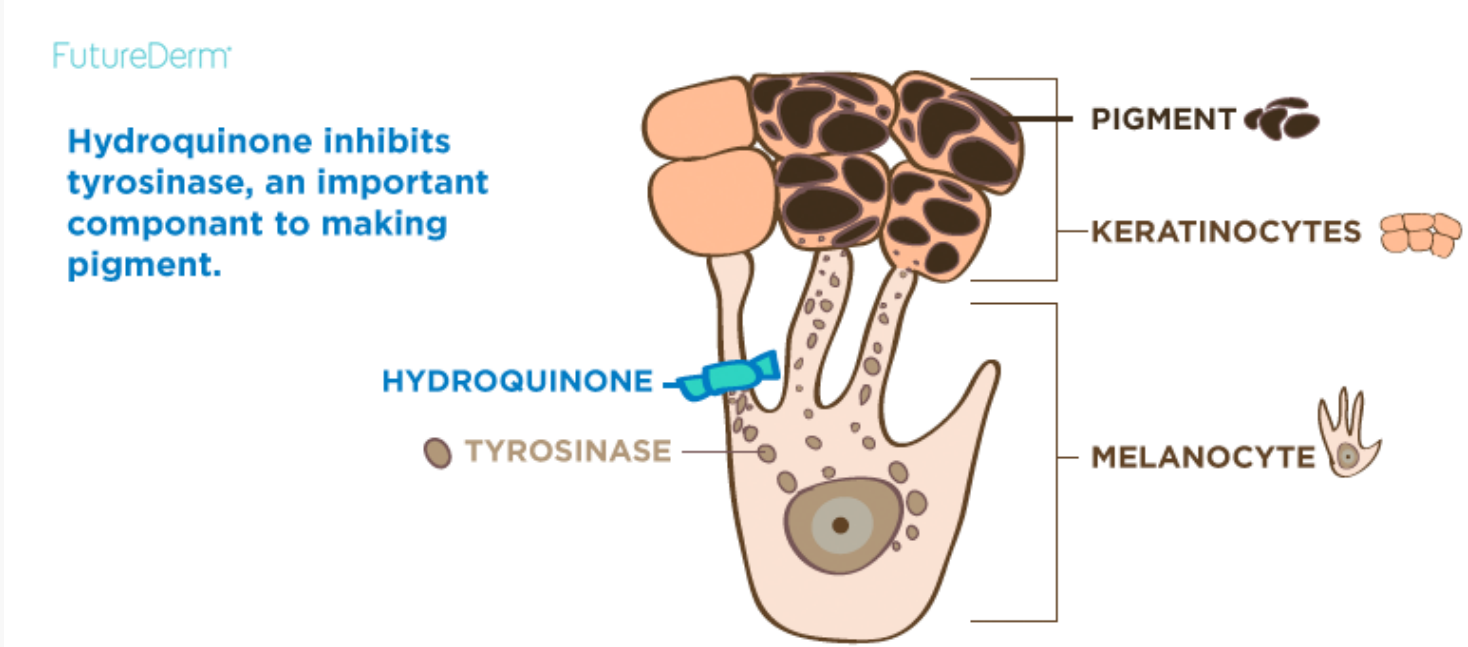
Part 1 - Topical therapies

❑ Hydroquinone :

- ➢ **as first-line** agent, both as monotherapy and combined with other agents.

- ➢ act by **inhibiting tyrosinase** :
  - by binding to the enzyme
  - by interaction with copper molecules at the enzyme's active site.

- ➢ **cytotoxic metabolites** of hydroquinone → interference with melanocyte function and viability .



- can be applied either in **cream** form or as an **alcohol-based solution**
- **Concentrations** → from 2% to 5%
- **hydroquinone in low concentrations (2%)** → similar or even inferior efficacy to other depigmenting agents (e.g., 20% azelaic acid).
- **the use of concentrations >5%** → associated with a high risk of various adverse events, including ochronosis, contact dermatitis, or even nail discolorations.
- The **optimal** concentration as monotherapy → **3%–4%** in terms of safety and tolerability
- The **combination** of hydroquinone, tretinoin, and steroid → more effective

hydroquinone 4%, retinoic acid 0.05%, and fluocinolone acetonide 0.01%

- Active only in **epidermal melanocytes** → inactive for **dermal melanophages**.
- The **efficacy** of HQ is related to → its concentration, the vehicle used, and chemical stability.
- The use of **3%–5% HQ** is recommended for → melasma treatment
- lower concentrations of **2%** → as maintenance therapy.
- If no improvement after **2 months** of therapy → treatment should be **discontinued**.
- In general, treatment with hydroquinone should be continued for → **at least 3m and up to 1y**.

➢ Adverse events :

- **Mild skin irritation**, itching, burning, stinging, contact-type dermatitis,
- **phototoxicity**, followed by secondary post-inflammatory hyperpigmentation (PIH),

(more frequent with formulations containing higher concentrations.)

- Chronic use of high concentrations of hydroquinone (≥5%) →
  - exogenous ochronosis
  - colloid milium,
  - localized vitiligo

(especially in patients with darker skin phototypes, and misuse or excessive use)

banning of the free use of hydroquinone as a cosmetic ingredient in several European countries, in which it can now only be used as a prescription drug.

- Another concern regarding hydroquinone use is → a **potential carcinogenicity**

hydroquinone, when administered **orally** → metabolized by the liver → produce benzene derivatives, which are known carcinogens (bone marrow toxicity and an antiapoptotic effect)

topically applied hydroquinone → bypasses the liver initially and is mainly metabolized via water-soluble, renally excreted molecules.

There have been **no reports to date of skin or internal organ malignancies** occurring in humans as a result of topical hydroquinone application

- Although it is maintained that the risk of developing a malignancy attributed to the topical use of hydroquinone is only theoretical and that the possibility or the appearance of an adverse event, such as ochronosis, is exceedingly low

topical preparations of hydroquinone should be administered as prescription drugs and **under the supervision of a trained physician**.

- Hydroquinone is a **class C drug** → should not be used during pregnancy

❑ Retinoids :

- The exact **mechanism of action** of retinoids, when used as depigmenting agents, is not yet fully understood.

↓

increased epidermal cell turnover
an inhibitory effect on tyrosinase.

- However, a **bimodal function** → by stimulating (induces melanocyte proliferation) and inhibiting (increases apoptosis of mature melanocytes) melanogenesis at the same time in murine models.

- Tretinoin has been evaluated in the treatment of → melasma, solar lentigines (and/or solar elastosis) and PIH :

  - **Solar elastosis and pigmentation** → a beneficial effect in wrinkling, tactile roughness, and mottled hyperpigmentation as well as in lentigines

- Given the **longer treatment** time needed to see a clinical benefit and the frequent occurrence of **irritation**, tretinoin may not be very useful as monotherapy for melasma and solar lentigines, while no specific recommendations can be made for the treatment of PIH.

- when used in **combination** → acts **synergistically** by increasing the absorption of other depigmenting agents, while still maintaining its own depigmenting properties.

It acts by removing melanin via keratinocyte shedding, enhances the penetration of HQ, and prevents the oxidation of HQ.

- Tretinoin is available in three forms: gel, cream, and liquid, at strengths ranging from **0.01% to 0.1%.**

- The most common **side effects** of tretinoin include : (retinoid dermatitis)
  - burning or stinging,
  - erythema,
  - scaling,
  - dry skin
  - photosensitizing effect

The dose must be adjusted to prevent inflammation,
Avoidance of sun exposure and proper sun protection

- **Class X** → should not be administered during pregnancy.

❑ Corticosteroids :

➢ In general, corticosteroids have not been found to be very effective in the treatment of hyperpigmentation when used as **monotherapy.**

↓↓↓

when used in combination therapies, besides exhibiting a **mild depigmenting potential**, also play an important role by **suppressing the inflammation** caused by the retinoids.

➢ Various corticosteroids have been used in triple-combination formulations :

- dexamethasone,
- hydrocortisone 1%,
- mometasone,
- fluorinated steroids (such as 0.01% fluocinolone acetonide).

➢ Side effects :

- Steroid-induced acne → **rosacea-like eruption** with persistent erythema, pustules, and papules →→ may **flare** if the corticosteroids are withdrawn abruptly, but usually improves after **1–3 months**.
- **Perioral dermatitis**
- **allergic contact dermatitis**
- **Skin atrophy and telangiectasia** → after long-term use.

➢ Fluorinated steroids → superior to non-fluorinated steroids, both in efficacy and in safety.

❑ Azelaic acid :

- a naturally occurring saturated **dicarboxylic acid** → derived from Pityrosporum ovale → a reversible competitive **inhibitor of tyrosinase**.

- an effective treatment for melasma → can be considered for patients that are **intolerant to HQ.**

- rather ineffective in the treatment of **solar lentigines**.

- beneficial in the treatment of acne-associated **PIH**

- **The adverse events** → generally mild :
  - pruritus,
  - mild erythema, and burning
  - scaling,

- can be used **in conjunction with retinoids**

- Pregnancy → **class B**

❑ Kojic acid :

- naturally produced by Aspergillus and Penicillium spp. → used widely as a depigmenting agent in numerous formulations.

↓↓

a **tyrosinase inhibitor**

upregulate interleukin-6 in keratinocytes → **inhibiting melanin production**.

- in concentrations ranging from → **1% to 4%**
- as monotherapy → **modest results** in the treatment of melasma
- as an alternative treatment for patients **not responding to treatments with HQ or AA.**

- **a known sensitizer** → its use has been strongly associated with adverse events such as burning sensation, erythema, and contact dermatitis.

↓↓↓

must be used with caution
Avoidance of sun exposure

❑ **Ascorbic acid (**vitamin C) **:**

- **a tyrosinase inhibitor**
- **moderate efficacy** in the treatment of melasma as monotherapy.
- a highly **unstable molecule** → rapidly oxidized →→ is better used in combination with other depigmenting agents such as GA, KA, licorice extracts, or soy.
- mild adverse events and is overall considered **safe** → an alternative therapy

❑ Arbutin :

- Arbutin and deoxyarbutin are → β-d-glucopyranoside **derivatives of hydroquinone**.
- Arbutin → **a naturally derived compound** → extracted from dry leaves of various plants such as bearberry, blueberry, and cranberry plants and pear trees.
- Deoxyarbutin → **a synthetic derivative** of hydroquinone → a **higher inhibitory** ability for tyrosinase compared to that of arbutin, but **10-fold lower** than that of hydroquinone but **less cytotoxic** than hydroquinone.
- used in **concentrations of 3%** → caution is suggested since its use may cause **paradoxical hyperpigmentation**.

- **Cysteamine** → a degradation product of the **amino acid L-cysteine**

- **Topical Methimazole** → a potent **peroxidase inhibitor** that blocks melanin synthesis

↓↓↓

Used in treatment of melasma and PIH

- **Topical Flutamide** → a nonsteroidal **antiandrogen**

Part 2 – Topical and systemic therapies

❑ Tranexamic acid :

- **a fibrinolytic inhibitor** agent → blocks the conversion of plasminogen to plasmin → impedes the binding of plasminogen to keratinocytes → diminished **arachidonic acid** release → decreased prostaglandin and fibroblast growth factor synthesis.

↓↓↓

Prostaglandins and fibroblast growth factor both stimulate **melanin synthesis**.

- TA also **decreases mast cells and angiogenesis**.

- TA is currently used via a spectrum of **delivery routes** including :
  - oral,
  - topical,
  - intradermal,
  - microneedling.

- The current **oral dosing** for melasma → significantly less than doses used to treat hemophilia, heavy menstrual bleeding, or other hemorrhagic conditions → **250 mg twice daily**

- Four studies specifically looked at the efficacy of PO TA dosed either at 250 mg BD or TDS → strong evidence that PO TA either dosed BD or TDS and **combined with HQ 4%** is very effective at improving melasma significantly over **12-16 weeks.**

- The lightening effect of 250 mg BD dosing → can be seen **as early as 2 months** into therapy.

- The risk of **relapse** → high when TA is discontinued → perhaps TA therapy should be considered more of a **long-term treatment**.

- General concerns → TA's propensity to induce thromboembolic phenomena →→ TA is contraindicated in patients with clotting disorders or a history of thromboembolism.

- Other **adverse events** related to **oral** TA use include :
  - mild gastrointestinal discomfort,
  - mild elevations in alanine transaminase levels
  - hypomenorrhea,
  - allergic skin rashes,
  - alopecia

- **Topical:**
  - erythema,
  - scaling,
  - dryness

❑ Melatonin :

- The hormone melatonin, which is secreted by the pineal gland, is **a potent antioxidant** and free-radical scavenger that stimulates several antioxidant enzymes, including superoxide dismutase, glutathione reductase, and glutathione peroxidase.

- Melatonin also **inhibits α-melanocyte-stimulating hormone receptors**.

- **Oral and topical melatonin** were evaluated in a series of 36 patients with melasma → all patients demonstrated a significant **reduction in MASI score** → glutathione (GSH) levels increased and suggest significant **improvement in oxidative stress**.

- AE: Not reported

❑ Glutathione :

- GSH is one of the **most powerful endogenous antioxidants** produced by cells in the human body and is a tripeptide of glutamate, cysteine, and glycine.

- **Mechanisms** that induce lightening of the skin include :
  - **inhibition of tyrosinase**
  - the ability to skew production of **eumelanin to pheomelanin**.

- There has been enormous recent publicity with regard to the use of intravenous GSH for general skin lightening →→ **Intravenous use of GSH has been associated with severe life-threatening reactions including Stevens–Johnson syndrome and anaphylaxis**.

.

➢ Several studies have evaluated oral and topical GSH for general skin lightening

↓↓

In an 8-week study, Handog et al. (2016) treated 30 healthy Filipino women with a **500 mg** buccal glutathione lozenge. The **melanin index** showed a significant reduction, and global assessments reported moderate lightening in 90% of subjects .

A **topical glutathione 2%** suspension was assessed in a randomized, double-blind, split-face, 10-week study, in which GSH was applied to one side and a placebo to the opposite side. The melanin index was significantly reduced in the GSH-treated side (Watanabe
et al., 2014).

➢ **AE:**

- **Intravenous** →→ Stevens-Johnson Syndrome, anaphylaxis
- **Oral and topical** →→ none

Part 3 - Chemical peels

- The chemical peels used for the treatment of hyperpigmentation disorders → by causing a controlled destruction of the **superfcial** part of the epidermis →→ **removal** of the unwanted excess pigment.

- **Superficial** chemical peels → generally effective for the management of **PIH and melasma** when properly applied in **fair-skinned** patients →→ **not be used for darker skin types**

- **Standard options** include :
  - glycolic acid 20-70%,
  - salicylic acid 20-30%,
  - trichloroacetic acid (TCA) 10-25%,
  - Jessner's solution.

- **Pretreatment** with a course of hydroquinone 4% topically → thought to improve outcomes.

- Any patient using **topical retinoids** → should discontinue their use **for seven days** prior to the peel.

- Continue to use → a noncomedogenic, sun protection factor **(SPF)** moisturizer.

❑ Alpha hydroxy peels :

- **GA and lactic acid** peels → are some of the most commonly used peels in the treatment of melasma.

- **Superficial to medium-depth** peels depending on → the concentration used, number of layers applied, and the duration of the application.

- GA peels are generally safe → with only mild adverse events include :
  - erythema
  - mild exfoliation
  - **PIH** → especially in darker phototypes

↓↓↓

high-concentration GA peels (>50%) should be avoided in dark-skinned patients.

❑ Beta hydroxy peels :

- **Salicylic acid** → an **anti-inflammatory** agent and has been shown to possess a depigmenting potential in a small number of trials.

- SA peels may be beneficial → in patients with **PIH attributed to acne**.

- **Adverse effects** → generally mild, including :
  - crusting,
  - transient hyperpigmentation and hypopigmentation,
  - temporary dryness.

Common lightening agents for melasma

Name	Mechanism of action	Side effects
Hydroquinone	Tyrosinase inhibition	Erythema, irritation, exogenous ochronosis
Azelaic acid	Tyrosinase inhibition	Stinging, burning, itching, dryness
Kojic acid	Tyrosinase inhibition	Irritation, contact dermatitis
Ascorbic acid	Inhibition of reactive oxygen species	No significant adverse event
Retinoids	Downregulation of Tyrosinase	Irritant reaction, dryness, hyperpigmentation
Corticosteroid treatments	Antiinflammatory and nonselective inhibition of melanogenesis	Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation
Niacinamide	Inhibition of melanasome transfer	Irritation
Licorice	Melanin dispersion, tyrosinase inhibition	No significant adverse event
Undecylenoyl phenylalanine	Antagonist of α-melanocyte-stimulating hormone, β-adrenergic, stem cell receptors	No significant adverse event
4-N-butylresorcinol	Tyrosinase inhibition, antioxidant, antiinflammatory	Mild erythema and itching
Soybean	Inhibits melanosome transfer to keratinocytes	No significant adverse event
Arbutin	Inhibition of tyrosinase	Skin irritation
Glucosamine	Inhibition of tyrosinase activation	Skin rash
Mequinol	Inhibition of tyrosinase	Skin irritation, redness, peeling

Part 4 - Laser and light therapy

- **Lasers and intense pulsed light** → useful for the treatment of a wide variety of disorders characterized by the presence of cutaneous hyperpigmentation.

- Knowledge of the **lesion type and lesional histopathologic** characteristics are critical for the selection of an appropriate light-based therapy.

- less effective **as monotherapy** → best when combined with other treatments, like peels or topical therapy.

- IPL is best suited for → Fitzpatrick skin **types I-III** due to the risk of PIH or hypopigmentation in those of darker skin types (**low-fluence or fractionated IPL**)

- The rationale for use of **vascular lasers** (pulsed dye laser or copper bromide laser) for melasma was based on the observation of increased vascularization in melasma lesions, but they have shown mixed and controversial results.

Proposed therapeutic ladder for melasma based on literature review

↓↓↓

➢ First-line therapy

- Control of risk factors (photoprotection, Discontinue hormone treatments, or photosensitising medications)

- Topical anti-tyrosinase therapy combination, based
on HQ 4% and tretinoin for 3 mo

- PO tranexamic acid 250 mg BD for 3 mo

➢ Second-line therapy

- Combination of first-line treatments + Laser treatment: LFQS Nd:Yag or Picosecond laser

- Skin types I/II/III: consider adjunctive therapy with PDL with setting aimed at vessels only

➢ Third-line therapy

- Combination of first-line treatments + a series of chemical peels

❑ CONCLUSIONS :

- Acquired hyperpigmentation disorders are relatively common disorders, associated with significant psychological morbidity for patients, as they represent a visible **aesthetic problem**.

- Melasma, solar lentigines, and PIH are only a few of the hyperpigmentation disorders encountered in the dermatological everyday practice.

- Regardless of the etiology of the hyperpigmentations, patients should always be informed about the **importance of sun protection** and the fact that no treatment provides **permanent results**.

- All currently available treatment regimens need → **sufficient time** to yield results and must be combined with highly effective sun protective measures in order to prevent disease recurrence .

- Topical depigmenting agents, used alone or in combination with chemical peels or laser, can produce acceptable results in the treatment of hyperpigmentations.

- Dermatology , Edited by Jean L. Bolognia , Fourth edition : Elsevier, 2018, ISBN 978–0-7020–6275–9
- Stephen Wolverton, Jashin Wu - Comprehensive Dermatologic Drug Therapy-Elsevier (2020)
- Hyperpigmentation,Edited By Dimitris Rigopoulos, Alexander C. Katoulis, First edition
- P.E. Grimes et al. New oral and topical approaches for the treatment of melasma . International Journal of Women's Dermatology 5 (2019) 30–36
- Spierings, NMK. Melasma: A critical analysis of clinical trials investigating treatment modalities published in the past 10 years. J Cosmet Dermatol. 2020; 19: 1284– 1289. https://doi.org/10.1111/jocd.13182
- McKesey J, Tovar-Garza A, Pandya AG. Melasma Treatment: An Evidence-Based Review. Am J Clin Dermatol. 2020 Apr;21(2):173-225. doi: 10.1007/s40257-019-00488-w. PMID: 31802394.

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Triple combination therapy for Melasma

Saman A.Nasrollahi PharmD, PhD

Associate Professor of CRTSDL
Managing Director of *Janus* Pharm. Mfg. Co.

Lightening, Whitening, Bleaching & Brightening

DEFINITIONS

- **Skin Lightening & Whitening/Skin Bleaching:**

A common drug claim for OTC/ RX products containing Hydroquinone, as this is the only skin-lightening active ingredient that is recognized by the U.S. FDA.

- **Skin Brightening:**

Brightening is a term used throughout the skin care industry to classify formulations that brighten uneven skin tone and contain alternatives to hydroquinone. These alternatives can include botanicals, natural ingredients, peptides, and vitamins. Natural skin lighteners are also considered multifunctional ingredients that provide multiple benefits for the skin.

Combination products

Topical agents when combined:

1. have the ability to give better therapeutic results as they act on different stages of melanogenesis.
2. Combining agents can also reduce side-effects.

- **steroids reduce hydroquinone and retinoid induced irritation**
- **retinoids can counter steroid-induced atrophy**
- **combination agents can be used as stabilizers**

sunscreens are also often added to combination agents

Triple Combination

- As the gold standard in the treatment of hyperpigmentation disorders, hydroquinone is often combined with different agents including retinoids, corticosteroids, glycolic acid, kojic acid and ascorbic acid.

- In split-face trial comparing a combination glycolic acid and kojic acid preparation with a glycolic acid and hydroquinone preparation, authors found no statistically significant difference in clinical efficacy.

- For melasma, in one split-face trial, a gel containing glycolic acid, hydroquinone and kojic acid showed more improvement (60%) in patients than a gel that contained only glycolic acid and hydroquinone (47.5%).

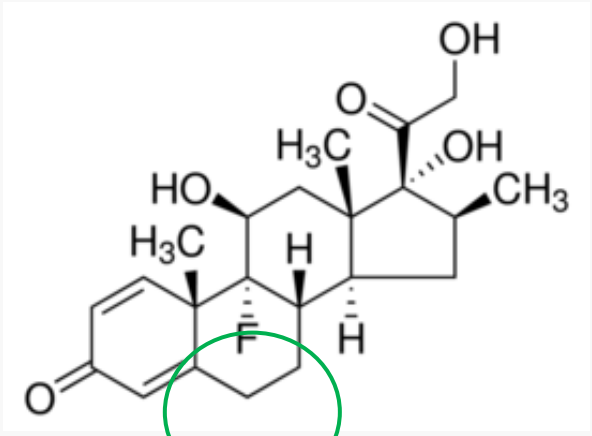
Triple Combination – Kligman Formula

- First proposed by Kligman and Willis, the original combination contained 5% hydroquinone, 0.1% tretinoin and 0.1% dexamethasone to be applied daily for 5 to 7 weeks, and it was found to be effective in the treatment of melasma.

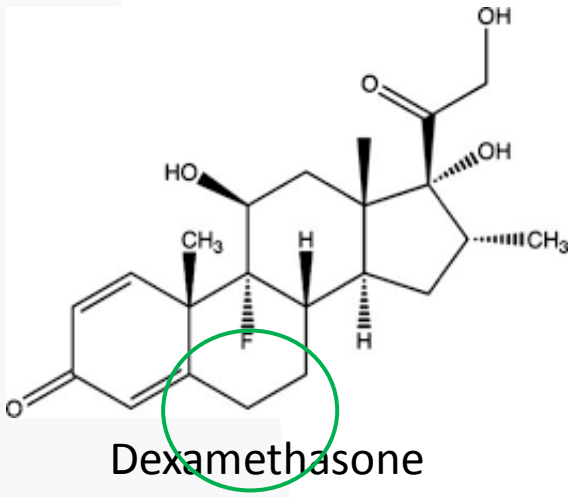
- Despite its effectiveness, this preparation contains high concentrations of TRE and HQ, and holds dexamethasone, which is a potent fluorinated steroid.

Triple Combination – Steroid comparison

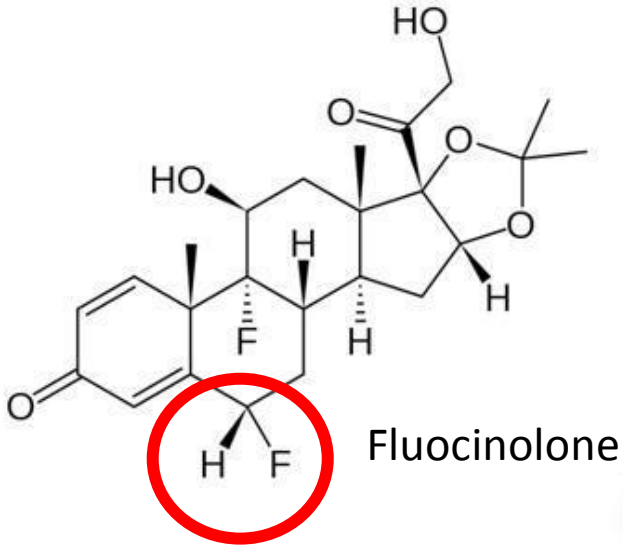
- **Dexamethasone and betamethasone (steroids 9-α fluorine) have no advantage over fluocinolone acetonide.**
- In fluocinolone acetonide halogenation in the 9-α position increases strength by improving target cell activity and reducing the conversion to inactive metabolites.



Betamethasone



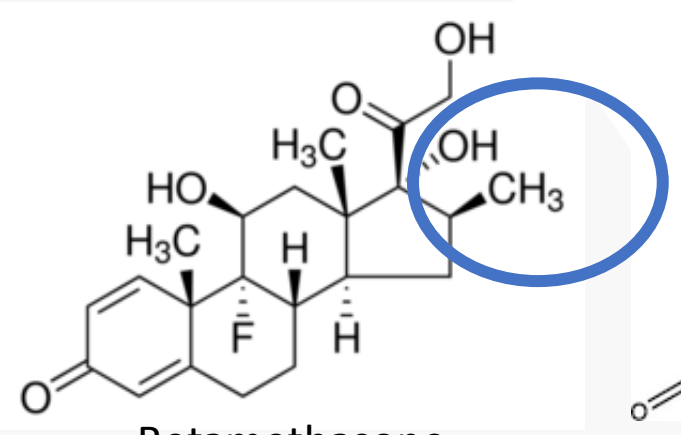
Dexamethasone



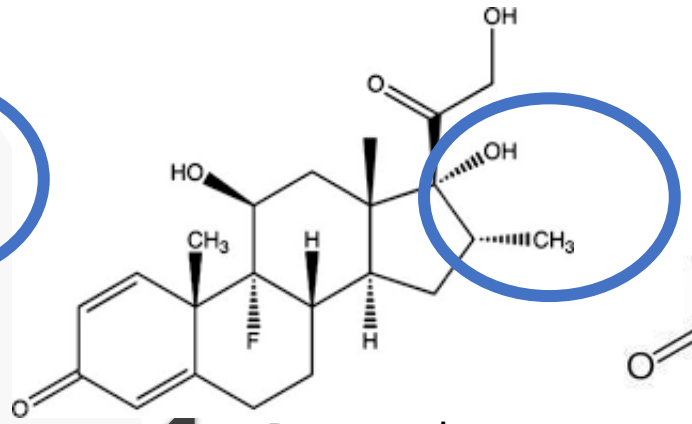
Fluocinolone

Triple Combination – Steroid comparison

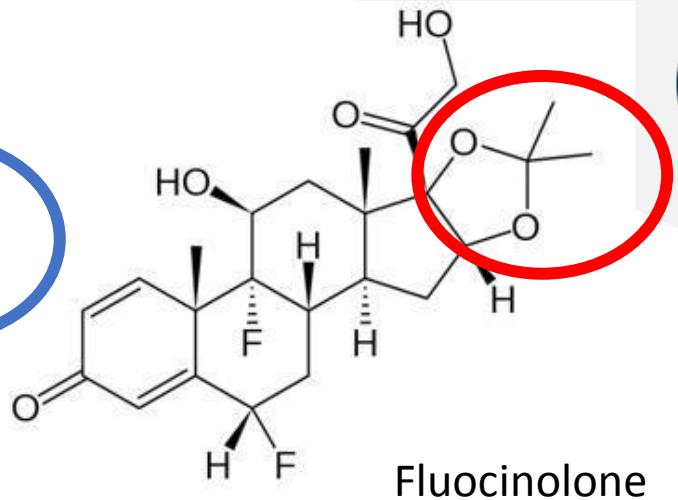
- Also, covering or removing the hydrophilic part in the position of 17 dihydroxy acetonide or 16-α-hydroxy, increases the lipophilicity of the molecule and thus increases the penetration in SC.



Betamethasone



Dexamethasone



Fluocinolone

Fluocinolone acetonide (fluorine steroids)

Superior corton in treatment of hyperpigmentation

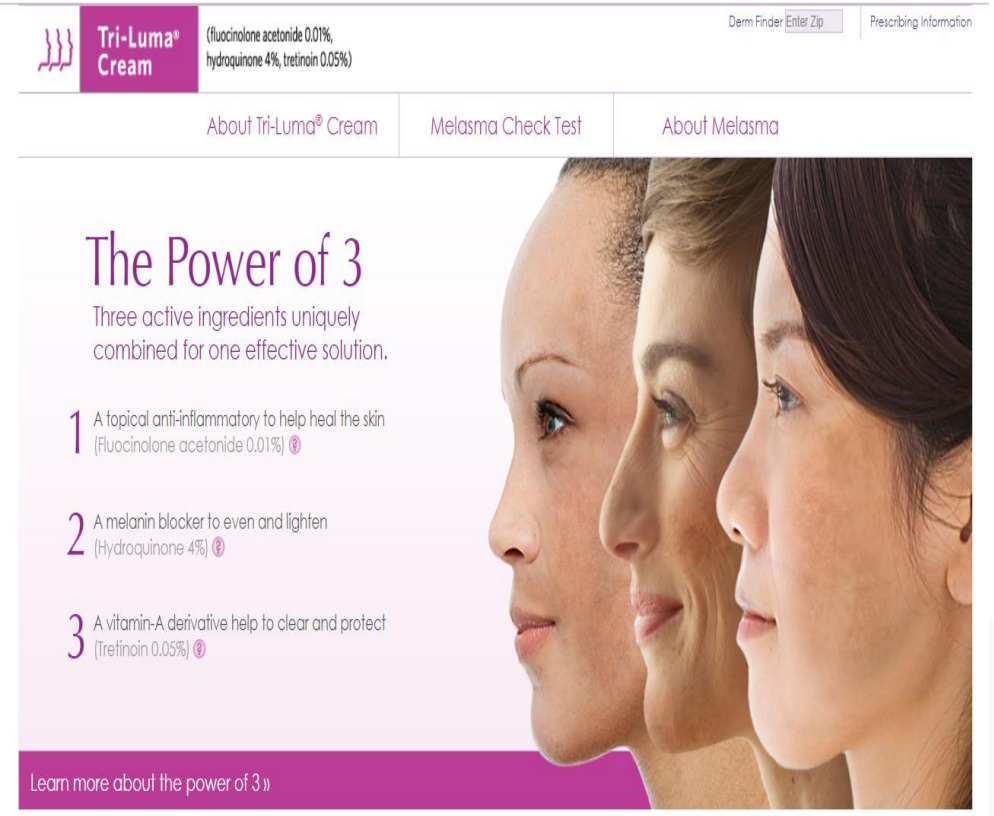
Triple Combination

- Therefore, the combination has been modified, fluocinolone acetonide added to reduce hydroquinone to 2–4% and tretinoin to 0.025–0.05%.

- Besides, use of regular photoprotection of at least SPF 15 has been shown to increase efficacy of topical therapy significantly.

One of the most **successful combination** formulations has been **4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide**.

In a multicentre, investigator-blinded, randomized, prospective trial in patients with melasma, this triple combination cream was found to be more efficacious than dual-combination creams containing either hydroquinone plus tretinoin,



Summary for TRI-LUMA

US Patents:	4
Applicants:	1
NDAs:	1

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Country	Document Number
Japan	2006507285
Poland	219020
China	1738587
Poland	
Slovenia	51
Brazil	0314882
Spain	2565317
Japan	4638234
Portugal	1562531
Canada	2503539

Expiration : 2025 & 2026


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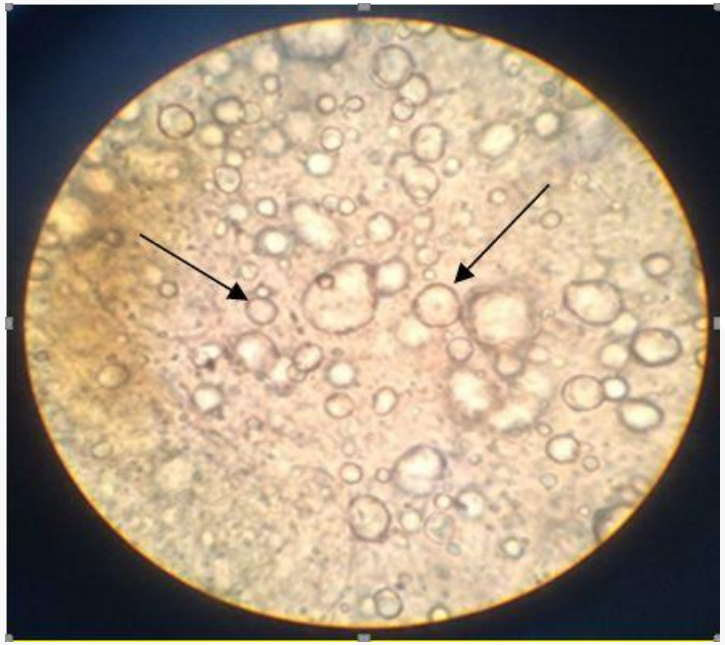
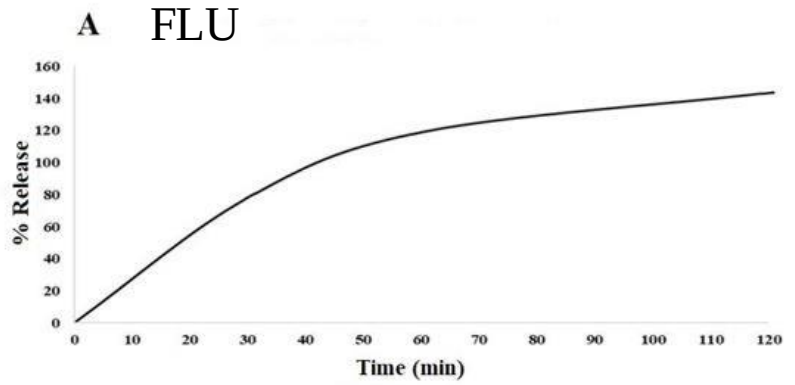
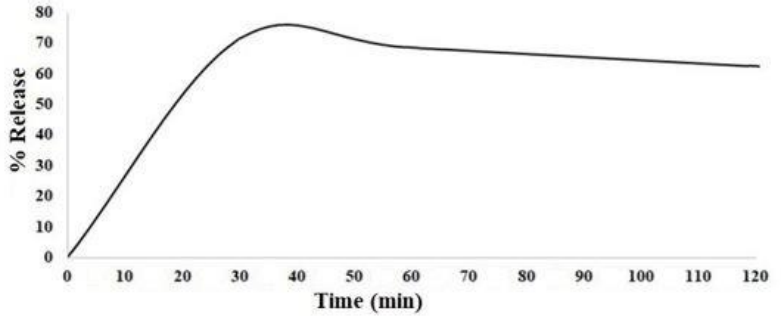
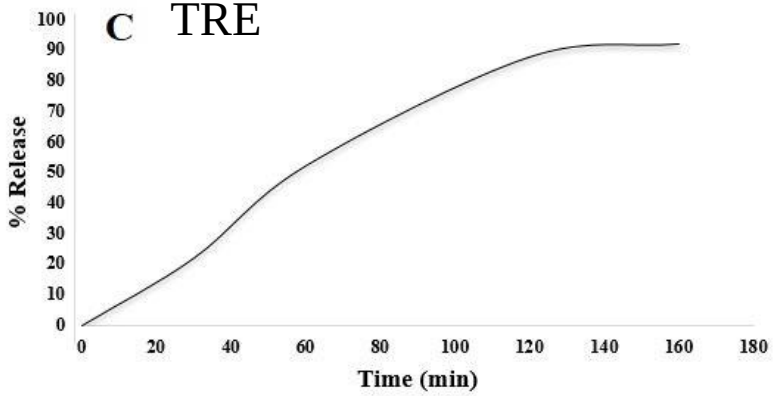








Cumulative drug release

Clinical study

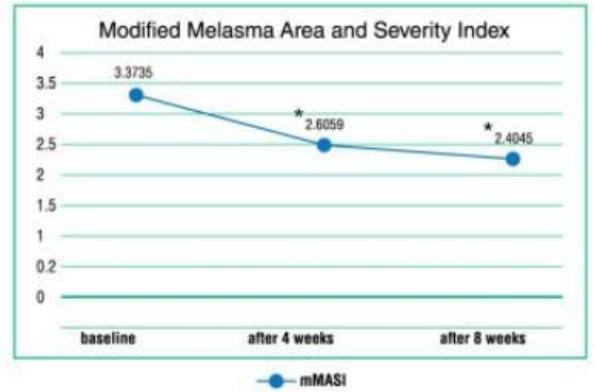
Clinical Trial
Phase IIb
Single group, before after clinical study

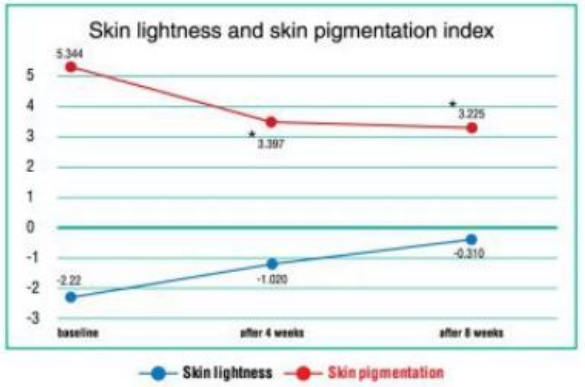
8 weeks Follow Up

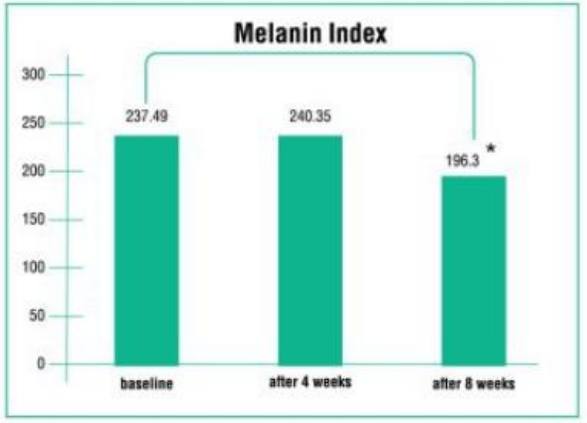
25 patients screened
22 patients enrolled
20 patients analyzed
Female
Age: 39.20 ± 4.16

Study Center
Tehran, Iran

Daily Application







*statistically significant compared to the baseline

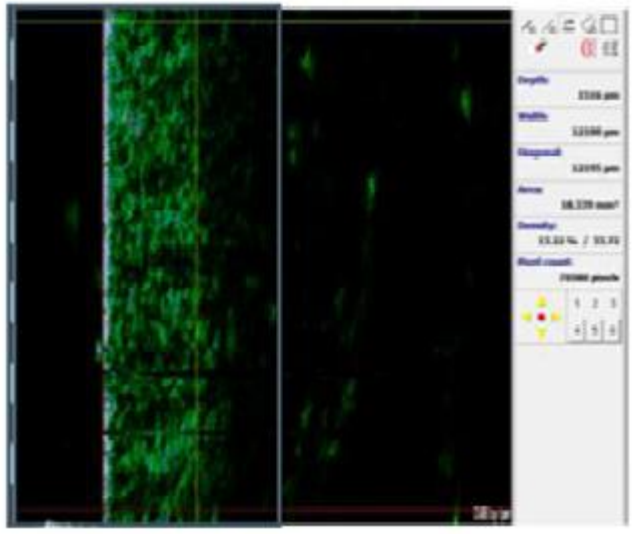
Comparison of changes in skin biophysical variables in baseline, 4 and 8 weeks after treatment

Variables	Baseline	After 4 weeks	After 8 weeks	p-value 1	p-value 2
TEWL	24.18± 13.03	30.70± 10.87	36.58± 17.01	0.087	0.000
Hydration	75.19± 16.51	76.54± 19.48	80.82± 15.50	0.770	0.317
Erythma index	385.85± 72.26	398.04±77.70	400.29± 67.20	0.352	0.292
sebum	22.42± 28.88	15.76± 12.22	8.88± 5.45	0.051	0.197
pH	6.93± 0.66	6.75± 0.67	7.03± 0.607	0.0687	0.417

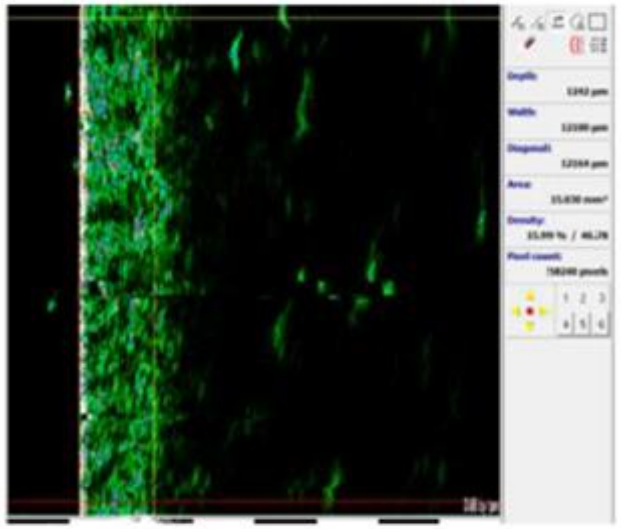
Comparison of ultra sonographic indices

Variables	Baseline	After 4 weeks	After 8 weeks	p-value 1	p-value 2
epidermis Thickness	132.99± 43.59	120.45±35.34	171.23± 240.62	0.177	0.586
Epidermal density	109± 55.13	201.96± 249.38	158.44± 163.64	0.101	0.312
Dermis thickness	1365.13± 234.30	1354.95± 261.37	1276.29± 193.74	0.889	0.524
Dermis density	27.56	31.41± 11.90	41.86± 20.25	0.329	0.029

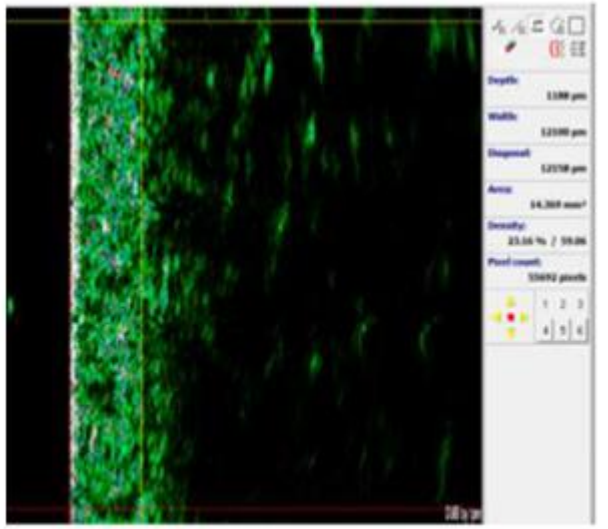
Comparison of ultra sonographic



Before



After 4 weeks



After 8 weeks

Maintenance

- **The reverting nature of melasma emphasizes the importance of maintaining efficacy achieved after triple combination treatment**.
- Kligman and Willis, the founders of a similar composition of TC therapy, observed that melasma relapse started as early as 1–2 weeks after cessation of treatment.
- The maintenance regimens could postpone melasma relapse by almost 5 months compared to the conventional cessation of daily.

Maintenance

➢Regime 1

- A study conducted by Arellano et al. (2012) demonstrated the **twice-weekly** triple combination regimen for **4 month** was more effective with a lower relapse on mild melasma, while the **tapering regimen (3 / week – 1st month, 2 / week –2nd and 3rd month, 1 / week – 4th month)** was more appropriate for those with moderate melasma.
- The result also confirmed that applying triple combination intermittently over a long time period is tolerable, safe and improver of the patient's quality of life.

Maintenance

➢**Regime 2**

- Grimes et al. in 2010 wrote that: Suggested maintenance regimen comprises 4% hydroquinone, tretinoin 0.05% and fluocinolone acetonide 0.01% applied twice weekly for 12 weeks.
- Wang et al. in 2019 said that: Triple combination was **applied daily for 8 weeks**, and in case of skin irritation, patients were allowed to **taper down to twice weekly in the following 6 weeks** and **once weekly in the final 6 weeks until** the final evaluation at **week 20**.

Another combination

- Pigmanorm cream; Louis Widmer GmbH, Rheinfelden, Germany
- Hydroquinone 5%, tretinoin 0.1%, hydrocortisone 1%

Another combination

- using 6% hydroquinone, 0.05% tretinoin, 0.05% triamcinolone acetonide and 0.1% ascorbic acid nightly with daily photoprotection was found to be efficacious, with five of six patients with epidermal or mixed melasma showing moderate to significant improvement **over an 8-week period**.

Another combination

- **6 month,** Azelaic acid (4%), Hydroquinone (1.6%) Methylprednisolone aceponate (0.04%), Salicylic acid (2%) nightly and not to wash till morning. In case of irritation, they were informed to use the mixture every other day in the first 2 weeks. Also all patients were strictly lectured to use a 50+ SPF

- **It is reported that mometasone or fluticasone containing combinations should be totally discouraged.**
- **Methylprednisolone aceponate (MPA),** a nonhalogenated TC with a methyl group at C6, confers higher intrinsic activity. As a fourth generation TC, MPA is included in the potent group. Several clinical studies supporting the use of 0.1% MPA with minimal local or systemic adverse effects have been reported. Compared with traditional TCs, MPA has an enhanced therapeutic index.

Side-effects of combination treatment

- ✓Erythema
- ✓Irritation
- ✓pruritus
- ✓Desquamation
- ✓cost

In a study by Kandhari and Khunger,[11] 69 patients with melasma were allocated to different combinations of tretinoin, corticosteroids and hydroquinone, individually and in combination, for varying durations. Erythema was reported in 43 patients (due to irritancy of hydroquinone), hypertrichosis in 30, telangiectasia in 25, acneiform eruptions in 18, rosacea-like-eruption in 13, epidermal atrophy in 2 and irritant contact dermatitis in 1 patient.[11] Sodium metabisulfite is a preservative found in hydroquinone formulations, which can cause hives, itching, wheezing, anaphylaxis and asthma exacerbations in susceptible individuals.[12]

➢ these side effects were transient and mild

Solution

- ✓Using a moisturizer in the morning
- ✓Using a sunscreen (SPF >30) during the day
- ✓Using a mild cleanser

Monotherapy or combination therapy?

- However, although associated with increased upfront costs, a cost/benefit analysis of combination therapy vs. hydroquinone alone for melasma found that the combination regimen led to a 30% greater rate of clearance with lower overall cost.

- Overall cost of combination therapy & monotherapy in USA 58$ & 114$
- In Colombia, Brazil, Chile & Argentina the cost of combination therapy vs. monotherapy is 30-50% lower

References

Clinical, Cosmetic and Investigational Dermatology

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CLINICAL TRIAL REPORT

Evaluation of the safety and efficacy of a triple combination cream (hydroquinone, tretinoin, and fluocinolone) for treatment of melasma in Middle Eastern skin

This article was published in the following Dove Press journal:
Clinical, Cosmetic and Investigational Dermatology

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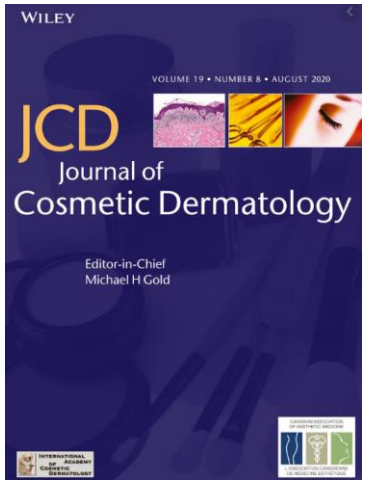
Background: Melasma is the most common pigmentary skin disorder, especially in females and those with darker complexion. The current study evaluated the safety and efficacy of a triple combination cream containing hydroquinone 4%+tretinoin 0.05%+fluocinolone acetonide 0.01% (Januluma® cream produced by Janus Pharmaceutical Co, Tehran, Iran) in the treatment of melasma.

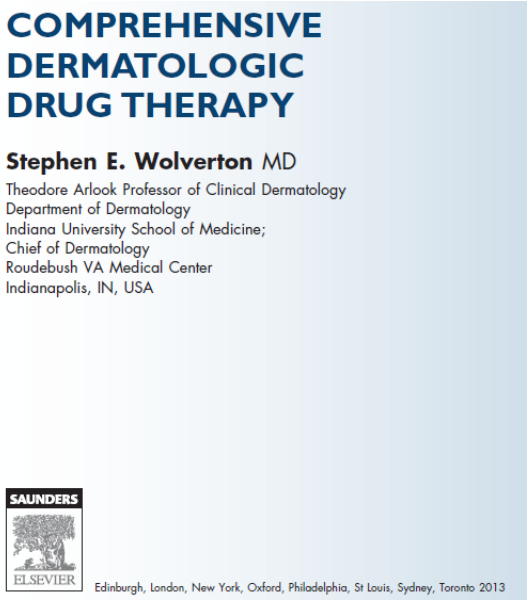
Patients and methods: Twenty-two female volunteers (mean±standard deviation of age: 39.20±4.16 years) who fulfilled the eligibility criteria participated in this study after signing the informed consent. They were requested to apply the Januluma® cream every night for 8 weeks. Modified melasma area and severity index (mMASI), skin lightness (L value), and severity of pigmentation (E value) by Visio Face, and skin biophysical parameters including pH, melanin index, erythema index, sebum, hydration, trans epidermal water loss, thickness and density of epidermis, and dermis (using 22 MHz ultrasonography) were measured before and 4 and 8 weeks after treatment. Also patients' satisfaction was assessed 4 and 8 weeks after treatment using visual analog score.

Results: mMASI decreased significantly from 3.37 to 2.60 at week 4, and to 2.40 at week 8 (*P*-values=0.00 and 0.01, respectively). Also, E and L values improved significantly after 8 weeks of treatment (*P*=0.01 and 0.00, respectively). Skin melanin index decreased from 237.49 AU to 196.30 AU at week 8 (*P*=0.01). Also echo density of dermis increased significantly after 8 weeks of treatment (*P*=0.029). Almost all participants experienced some degrees of pruritus, scaling, and erythema, esspecially during the first month of application, which were generally mild and tolerable. The mean satisfaction of patients with the treatment was 6.77.

Conclusion: The triple combination formula was reasonably safe and effective for treatment of melasma in Middle Eastern patients.

Keywords: melasma, combination therapy, efficacy assessment, Middle Easterners





References

طاقچه دسته‌بندی بی‌نهایت صوتی

طاقچه / منابع و مراجع / اطلاعات عمومی / آشنایی با فراورده‌های آرایشی و بهداشتی ۱

دانلود کتاب آشنایی با فراورده‌های آرایشی و بهداشتی ۱

نویسنده: سامان احمدنصراللهی > عاطفه نعیمی‌فر >
انتشارات سپید برگ

۱/۰ از ۲ نظر

آشنایی با فراورده‌های آرایشی و بهداشتی (۱)

تألیف و گردآوری: دکتر سامان احمدنصراللهی (عضو هیأت علمی دانشگاه علوم پزشکی تهران)، دکتر عاطفه نعیمی‌فر، دکتر بهناز دانشمند، دکتر کمند هدایت، دکتر انیسه صمدی، دکتر سارا بحرینیان، دکتر زینب خسروپور، دکتر زهرا قاسمی، دکتر سیدسجاد آل‌نبی

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همکار مرکز آموزش و پژوهش بیماری های پوست و جذام دانشگاه علوم پزشکی تهران

Novel treatment strategies for Disorders of Hyperpigmentation

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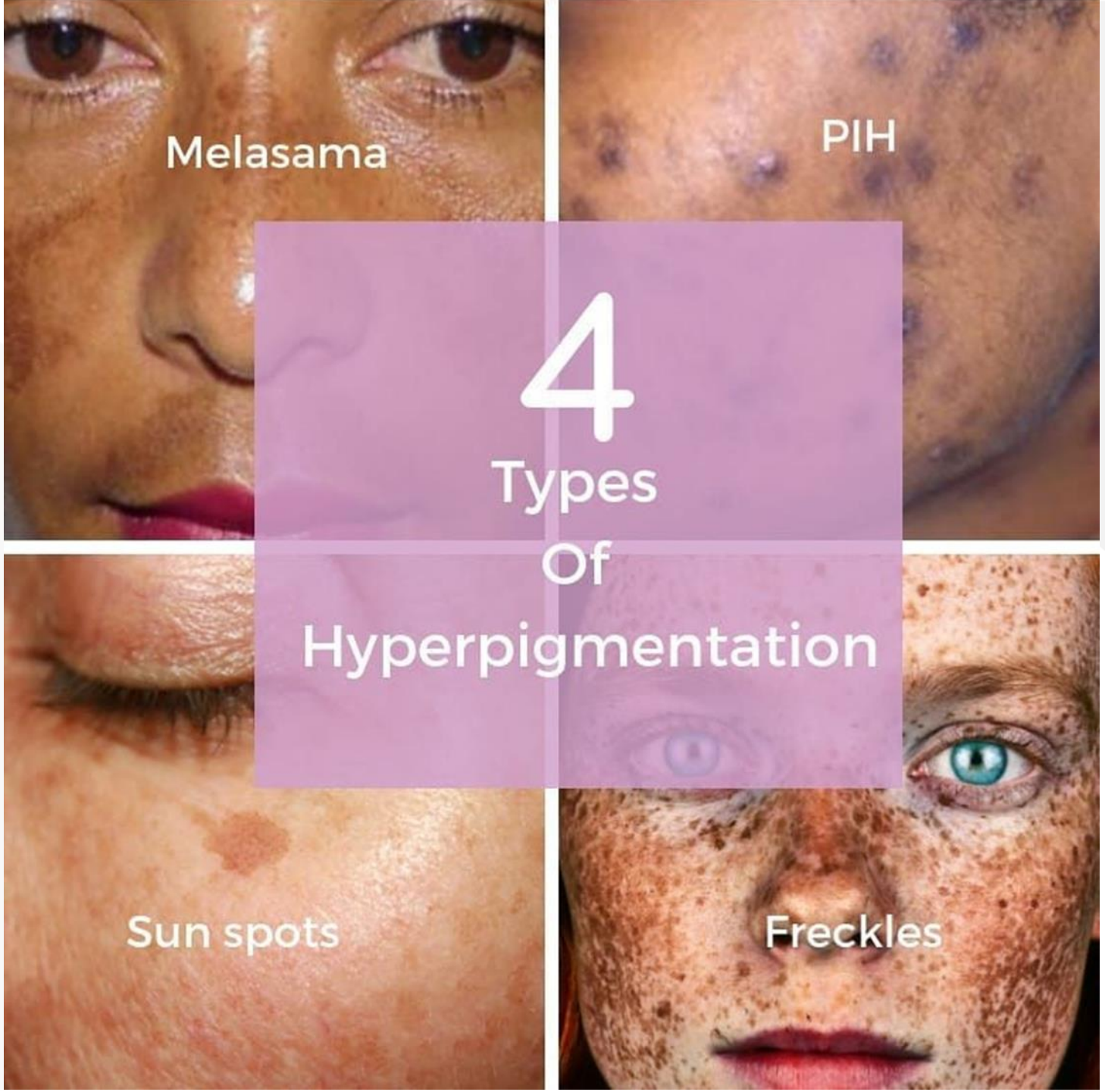
M.D. Dermatologist

Center for Research and Training in Skin diseases and Leprosy

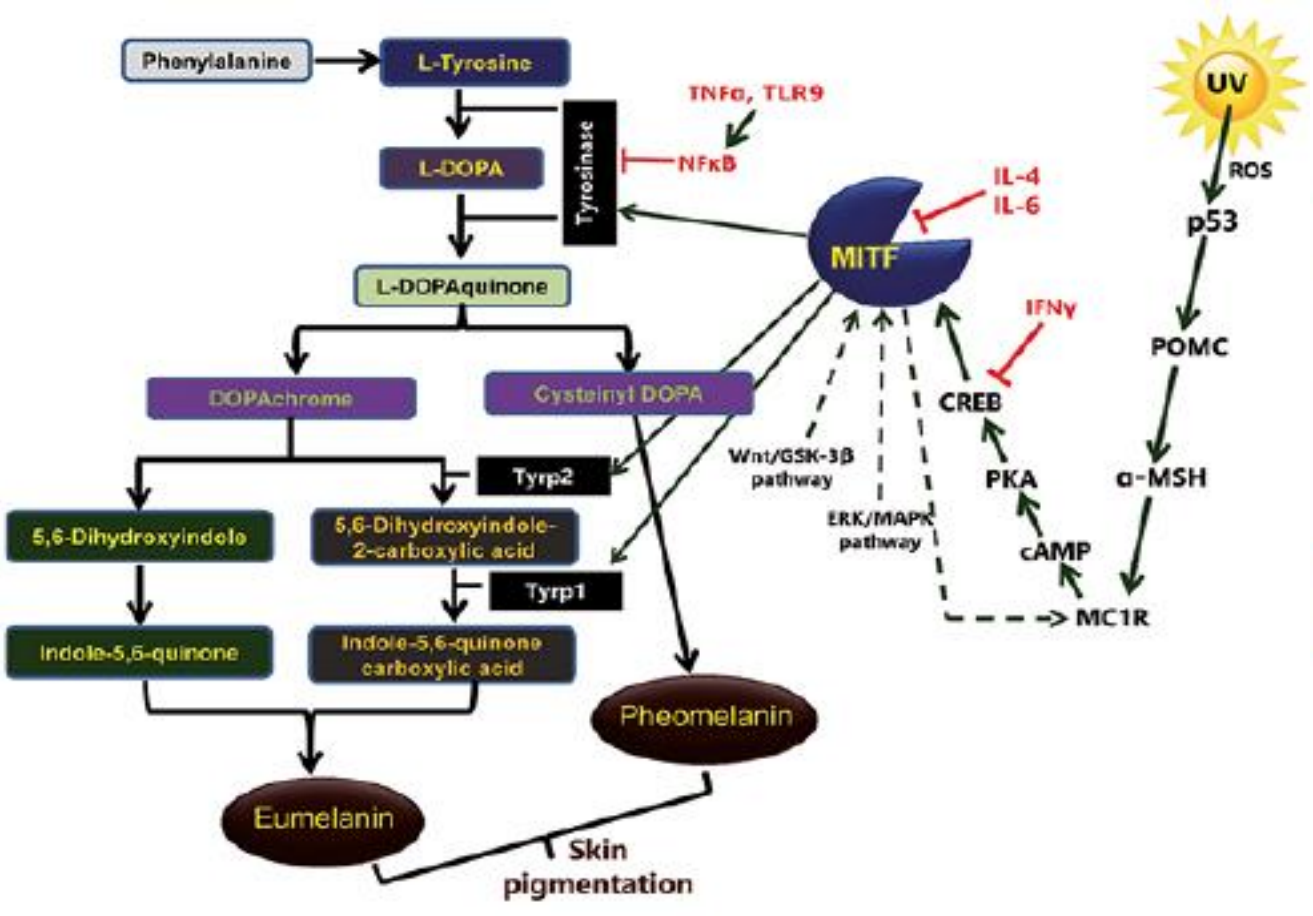

Melasama
PIH
4
Types
Of
Hyperpigmentation
Sun spots
Freckles

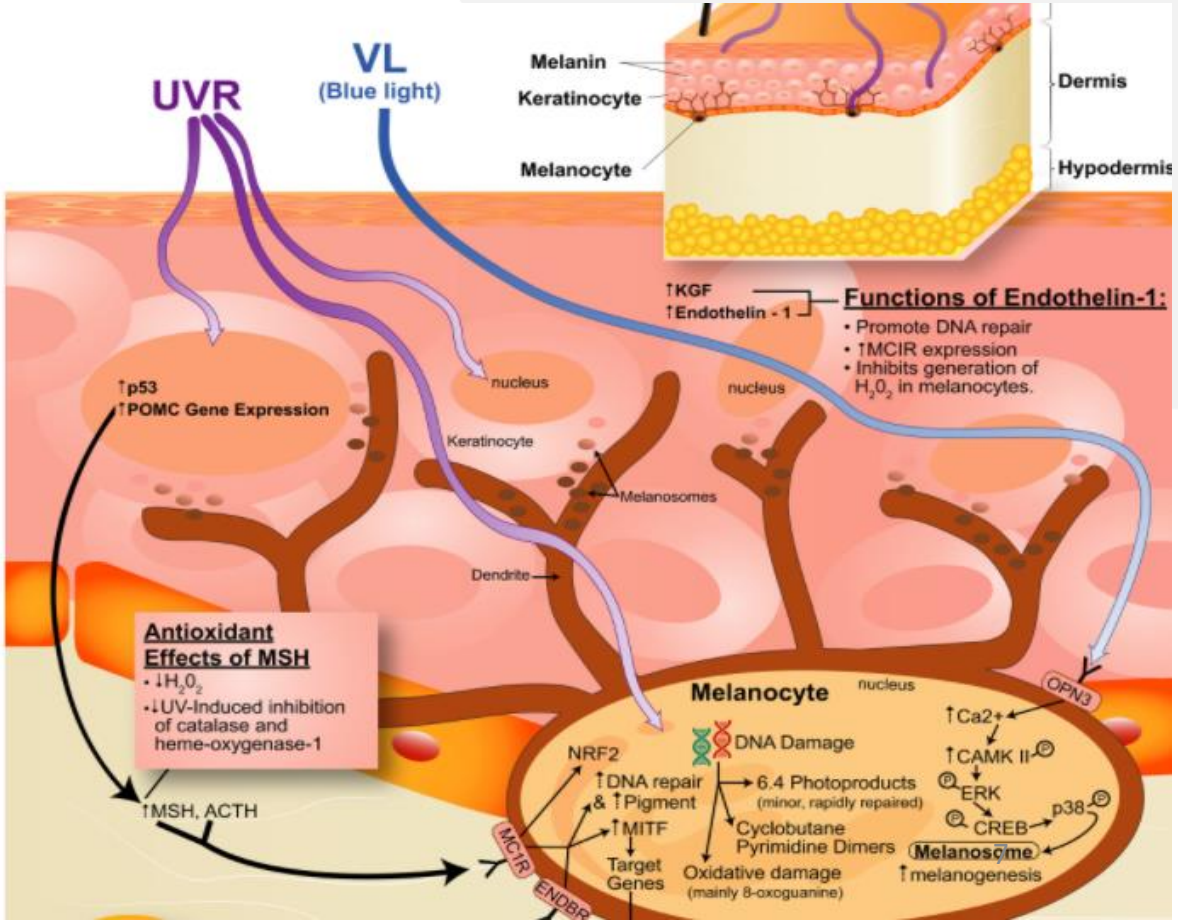

Topical Cream 15g
For external use only
Januluma®

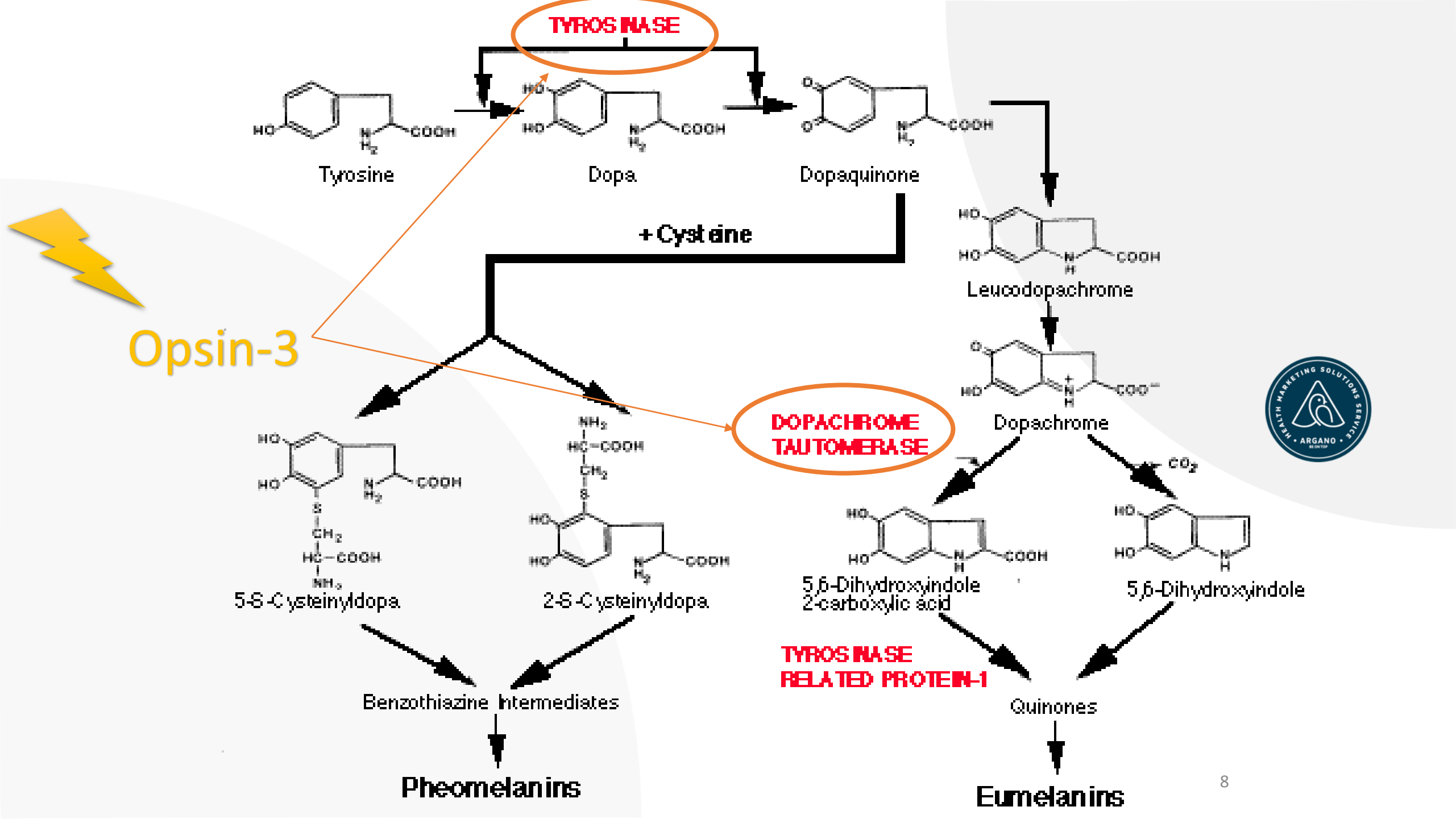
Photoprotection

The role of visible light

- In addition to the deleterious impact of UV light as a trigger and relapsing factor, recent studies have implicated a role for visible light.






TYROSINASE
Tyrosine
Dopa
Dopaquinone
+ Cysteine
Leucodopachrome
Dopachrome
DOPACHROME TAUTOMERASE
5-S-Cysteinyldopa
2-S-Cysteinyldopa
5,6-Dihydroxyindole 2-carboxylic acid
5,6-Dihydroxyindole
TYROSINASE RELATED PROTEIN-1
Benzothiazine Intermediates
Quinones
Pheomelanins
Eumelanins

Opsin-3

The role of visible light

- Tyrosinase and dopachrome form a protein complex that is mainly generated in the melanocytes of dark-skinned individuals.
- Visible blue light irradiation in individuals with darker skin types are thought to induce long-lasting hyperpigmentation.
- Photoprotection should incorporate visible light blockade.

Visible light Blocking agents

		Absorption			
		UVB	UVA2	UVA1	Visible
		290–320	320–340	340–400	400–800
Organic or 'chemical absorbers'					
	PABA derivates				
	PABA (para-aminobenzoic acid)				
	Padimate O (octyl dimethyl PABA)				
	Cinnamates				
	Ooctyl methoxycinnamate (Octinoxate, Parsol MCX)				
	Cinoxate				
	Salicylates				
	Octisalate (octyl salicylate)				
	Homosalate (homomethyl salicylate)				
	Trolamine salicylate				
	Benzophenones				
	Oxybenzone (benzophennne-3)				
	Sulisobenzone (benzophenone-4)				
	Dioxybenzone (benzophenone-8)				
	Others				
	Octocrylene				
	Ensulizole (phenylbenzimidazole sulfonic acid)				
	Enzacamene (4-methyl-benzylidene camphor (4-MBC), Eusolex 6300, Neo Heliopan® MBC)*				
	Ethylhexyl triazone (Uvinal® T 150)*				
	Avobenzone (butyl methoxydibenzoyl methane, Parsol 1789)				
	Menthyl anthranilate (meradimate)				
	Ecamsule (Mexoryl™ SX, terephthalylidene dicamphor sulfonic acid)				
	Drometrizole trisiloxane (Mexoryl™ XL)*				
	Bisoctrizole (Tinosorb® M, methylene-bis-benzotriazolyl tetramethylbutylphenol)*				
	Bemotrizinol (Tinosorb® S, bis-ethylhexyloxyphenol methoxyphenyl triazine)*				
	Diethyamino hydroxybenzoyl hexyl benzoate (Uvinul® A Plus)*				
	Bisdisulizole (Neo Heliopan® AP)*				
	Isotrizinol (Uvasorb® HEB)*				
Inorganic or 'physical blockers'**					
	Titanium dioxide				
	Zinc oxide				
Other agents (not considered active screens)					
	Dihydroxyacetone				
	Iron oxide				

Inorganic or 'physical blockers'**	
	Titanium dioxide
	Zinc oxide
Other agents (not considered active screens)	
	Dihydroxyacetone
	Iron oxide

There are few readily available iron oxide formulations, and optimally block UV light in the visible spectrum.

Visible light Blocking agents

Castanedo-Cazares et al:

- UV-only sunscreen (mexoryl SX, titanium dioxide, octocrylene, Tinasorb–S, and avobenzone) vs UV-visible light sunscreen with the same regimen plus iron oxide.
- Both with SPF≥ 50.
- 68 patients were included in this 8-week study
- Significantly greater improvement was observed in UV-visible light regimen.

Boukari et al.

- 6-month study of 40 patients
- UV–visible light sunscreen that contained iron oxide.
- The control group used the same UV sunscreen that provided the same UV-B and UV-A protection without the iron oxide.
- A significantly greater reduction in Melasma Area Severity Index (MASI) score

Polypodium leucotomos

- A fern of the Polypodiaceae family.
- Mechanism of Action:
  - Promotes the p53 suppressor
  - Modulates inflammatory cytokines
  - Upregulates endogenous antioxidant systems
  - Blockes UV radiation-induced cyclooxygenase–2 expression.

Polypodium leucotomos

Martin et al:

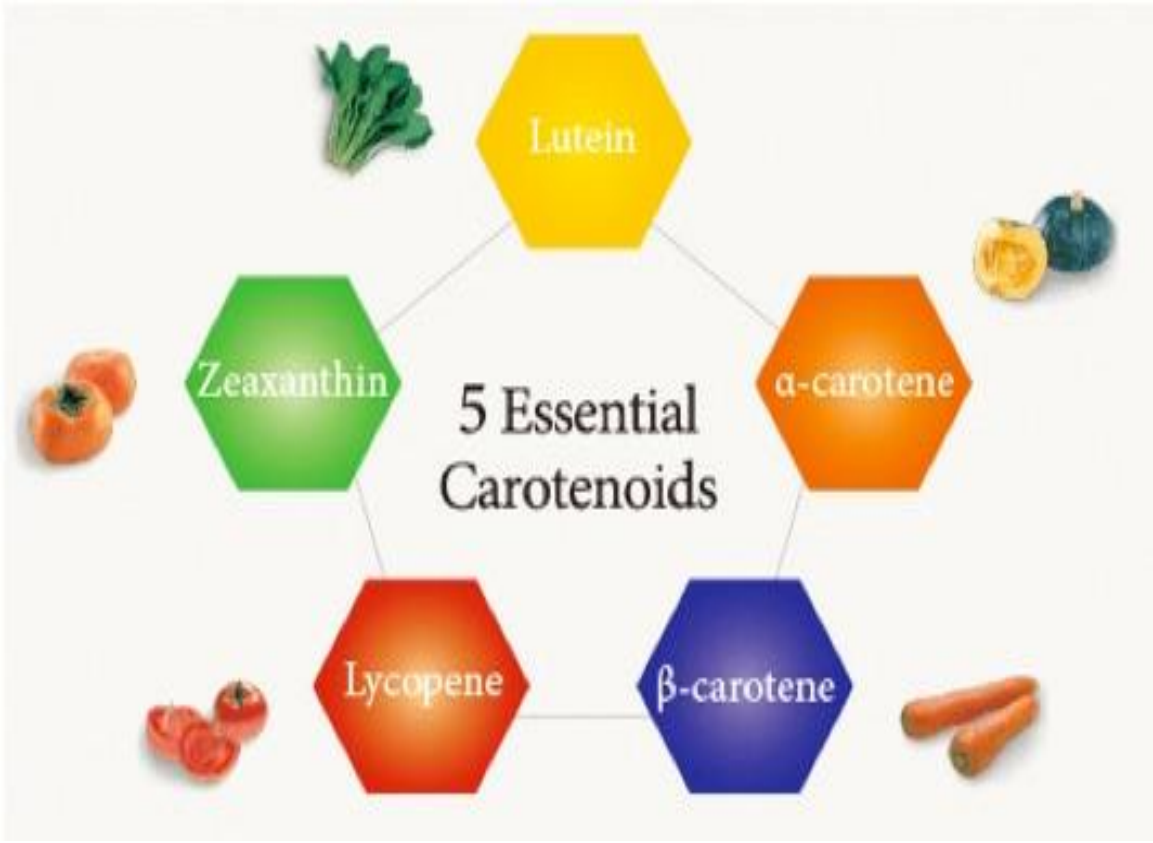
- Randomized, placebo-controlled study.
- 40 patients
- Oral PL 240 mg twice daily versus placebo.
- Reported a statistically significant effect.

Goh et al:

- Double-blind, placebo-controlled trial
- Oral PL 240 mg twice daily for 12 weeks +broad spectrum sunscreen+ hydroquinone 4% daily.
- The group treated with PL achieved a significantly greater reduction in MASI score at 56 and 84 days.

Carotenoids

- Naturally occurring pigments synthesized by plants, algae, and photosynthetic bacteria.
- Mechanism of Action:
  - Anti-inflammatory, antioxidant, and protection against photo damage
  - Carotenoids concentrate in the skin and are able to absorb UV radiation and work by scavenging reactive oxygen species.
  - Absorption spectra in both UVB and UVA range and are able to block the formation of melanin.



Carotenoids

Teo et al:

- Randomized, placebo-controlled study.
- 44 patients
- Oral carotenoid 800mg daily versus placebo for 80 days.
- Reported a statistically significant effect in reduction of both pigmentation and erythema.

Minimal concern of adverse effects with the most common side effect is skin color change, particularly at high dosages for prolonged periods of time, though reversible on discontinuation.

Photoprotection

Iron-oxide

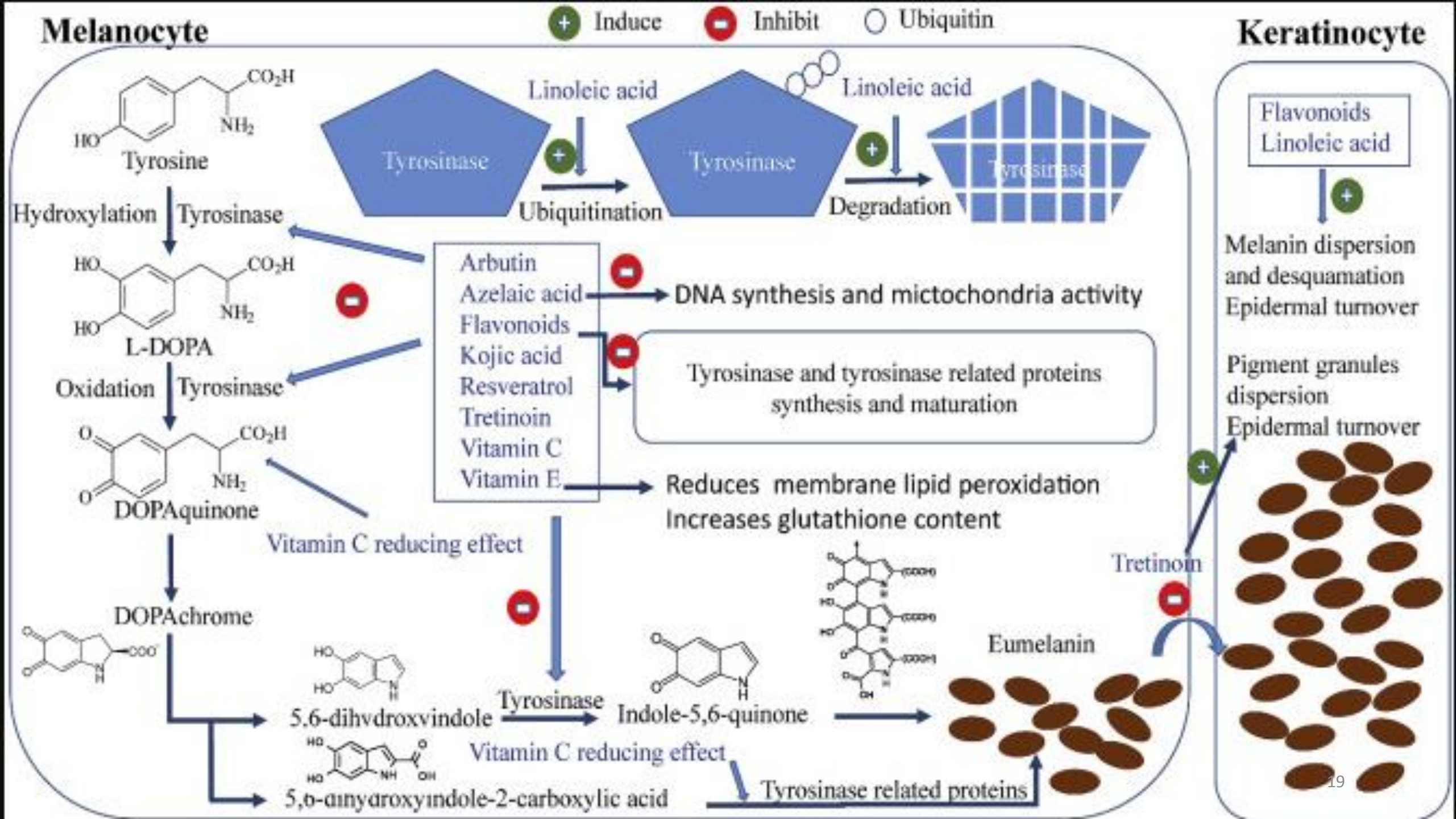
Polypodium leucotomos

Carotenoids

Whitening/ Lightening agents

Common lightening agents for melasma

Hydroquinone	Tyrosinase inhibition	Erythema, irritation, exogenous ochronosis
Azelaic acid	Tyrosinase inhibition	Stinging, burning, itching, dryness
Kojic acid	Tyrosinase inhibition	Irritation, contact dermatitis
Ascorbic acid	Inhibition of reactive oxygen species	No significant adverse event
Retinoids	Downregulation of Tyrosinase	Irritant reaction, dryness, hyperpigmentation
Corticosteroid treatments	Antiinflammatory and nonselective inhibition of melanogenesis	Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation
Niacinamide	Inhibition of melanasome transfer	Irritation
Licorice	Melanin dispersion, tyrosinase inhibition	No significant adverse event
Undecylenoyl phenylalanine	Antagonist of α-melanocyte-stimulating hormone, β-adrenergic, stem cell receptors	No significant adverse event
4-N-butylresorcinol	Tyrosinase inhibition, antioxidant, antiinflammatory	Mild erythema and itching
Soybean	Inhibits melanosome transfer to keratinocytes	No significant adverse event
Arbutin	Inhibition of tyrosinase	Skin irritation
Glucosamine	Inhibition of tyrosinase activation	Skin rash
Mequinol	Inhibition of tyrosinase	Skin irritation, redness, peeling


Melanocyte
Induce
Inhibit
Ubiquitin
Keratinocyte
Tyrosine
Linoleic acid
Tyrosinase
Ubiquitination
Linoleic acid
Tyrosinase
Degradation
Tyrosinase
Flavonoids
Linoleic acid
Melanin dispersion
and desquamation
Epidermal turnover
Hydroxylation
Tyrosinase
L-DOPA
Arbutin
Azelaic acid
Flavonoids
Kojic acid
Resveratrol
Tretinoin
Vitamin C
Vitamin E
DNA synthesis and mictochondria activity
Tyrosinase and tyrosinase related proteins
synthesis and maturation
Oxidation
Tyrosinase
DOPAquinone
Vitamin C reducing effect
Reduces membrane lipid peroxidation
Increases glutathione content
Pigment granules
dispersion
Epidermal turnover
Tretinoin
DOPAchrome
5,6-dihydroxyindole
Tyrosinase
Indole-5,6-quinone
Eumelanin
Vitamin C reducing effect
5,6-dihydroxyindole-2-carboxylic acid
Tyrosinase related proteins

Melatonin

Function:

- Potent antioxidant/free radical scavenger
- ↑ super oxide dismutase, glutathione reductase, glutathione peroxidase
- ↓ α-MSH receptors

Prescription:

- Topical 5% BID
- Oral 3 mg daily

Side effects:

- Oral and topical: none

Melatonin

Hammad et al:

- Combination of oral and topical melatonin
- 36 patients with melasma and 10 healthy controls
- Followed 90 days
- Resulted in a significant reduction in MASI score and significant improvement in oxidative stress.
- Results were inferior to hydroquinone.
- In general, oral melatonin is considered safe and well tolerated in adults in dosages up to 10 mg daily, as studied in sleep disorders.

Pinus pinaster (procyanidin)

Function:

- Many active compounds such as monomeric phenolic compounds, phenolic acids, and condensed flavonoids
- Anti-inflammatory properties
- Strong antioxidant
  - Several times more powerful than vitamins C and E,
  - It is also able to recycle vitamin C, regenerate vitamin E,
  - It also increases the endogenous antioxidant enzyme system

Prescription:

- Oral 24 mg twice daily

Side effects:

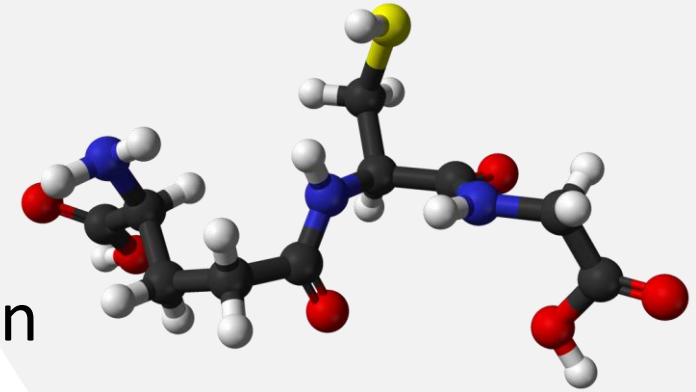
- metallic taste

Pinus pinaster (procyanidin)

Handog et al:

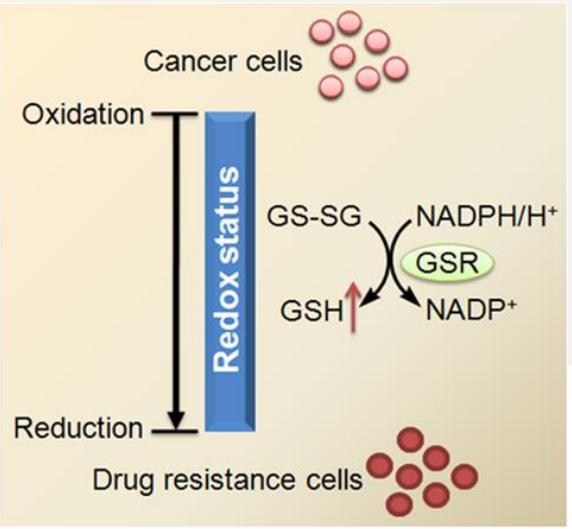
- Sixty female Filipino women with bilateral epidermal melasma
- oral procyanidin, 24 mg twice daily
- 8 weeks
- MASI scores Mexameter results showed a significant improvement in pigmentation.

GSH (Glutathione)



Function:

- Decreases tyrosinase
- Skews conversion of eumelanin to pheomelanin



Prescription:

- Topical 2% daily
- Oral 500 mg daily

Side effects:

- Intravenous: Stevens-Johnson Syndrome, anaphylaxis
- Oral and topical: none

GSH (Glutathione)

Handog et al:

- 30 healthy Filipino women
- 500 mg buccal glutathione lozenge
- 8-week study
- The melanin index showed a significant reduction in MASI score
- Global assessments reported moderate lightening in 90% of subjects

Watanabe et al:

- A randomized, double-blind, split-face
- Topical glutathione 2% suspension
- 10-week study
- The melanin index was significantly reduced.

Cysteamine

Function:

- Radio protector via direct scavenging effects of hydroxy radicals
- Tyrosinase peroxidase inhibition

Prescription:

- 5% daily

Side effects:

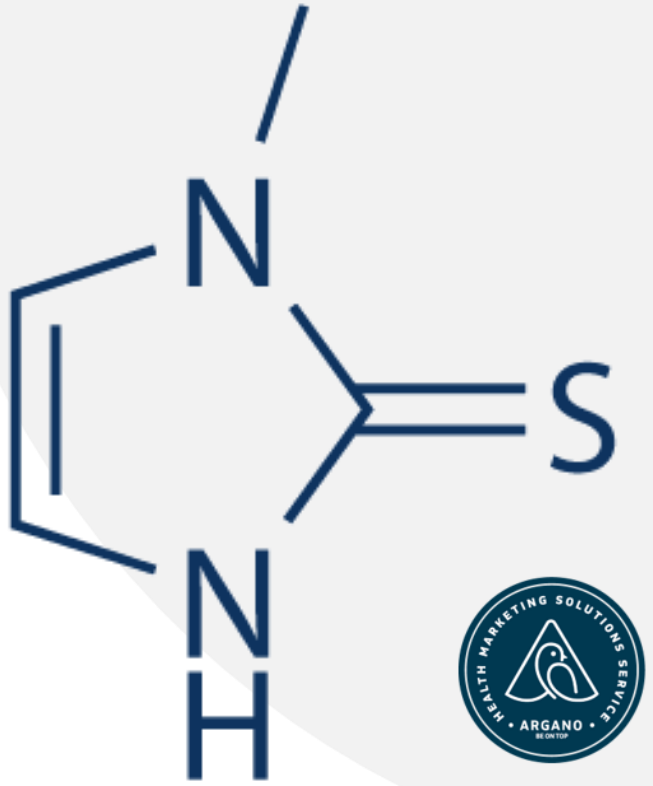
- None

Cysteamine

Mansouri et al.

- A randomized, double-blind trial
- 50 patients with melasma
- 5% cysteamine cream
- 16 weeks
- Cysteamine induced significant reductions in MASI scores.

Methimazole



Function:

- Used to treat hyperthyroidism
- Potent peroxidase inhibitor
- blocks melanin synthesis

Prescription:

- 5% daily

Side effects:

- No significant changes in serum TSH, free thyroxine, free triiodothymine levels
- Minimal cutaneous side effects

Methimazole

Kasraee et al:

- 20 patients with epidermal melasma
- Methimazole 5% was applied daily
- Significant reduction in MASI score
- No significant changes in serum thyroid-stimulating hormone, free thyroxine, and free triiodothyronine levels.
- Methimazole was well tolerated with minimal cutaneous side effects.
- Recommend that methimazole only be applied to areas affected by melasma and should not be used as a general cosmetic lightening agent.

Methimazole

Gheisari et al:

- Double blind RCT
- 50 patients
- 4% hydroquinone vs. 5% methimazole once daily for 8 weeks
- Both groups showed a reduction in the MASI score
- More significant in hydroquinone group
- Higher relapse rate was also observed in hydroquinone
- The side effects were similar between groups.

Flutamide

Function:

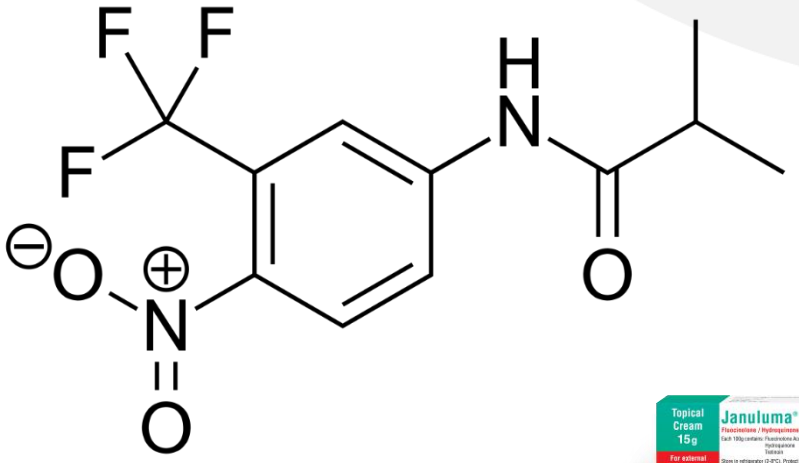
- Blocks action of endogenous/ exogenous testosterone by binding to androgen receptor

Prescription:

- 1% daily

Side effects:

- None



Flutamide

Adalatkhah and Sadeghi-Bazargani:

- Parallel, randomized RCT
- Once daily flutamide 1% vs. hydroquinone 4%
- 16-week
- The results of MASI and colorimetry scores revealed similar efficacy for flutamide and hydroquinone 4%.
- Patient satisfaction scores were significantly higher in the flutamide group.

Whitening/ Lightening agents

Melatonin
Procyanidin
Glutathione
Cysteamine
Methimazole
Flutamide

THANK YOU FOR YOUR ATTENTION

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