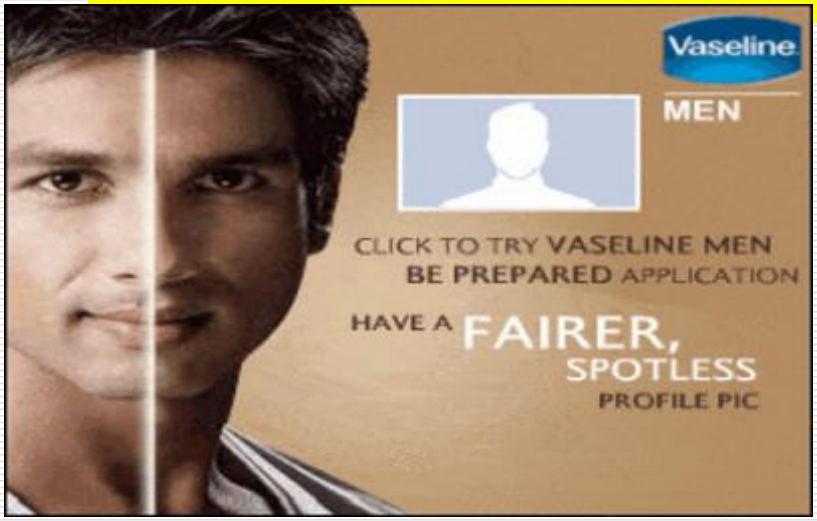
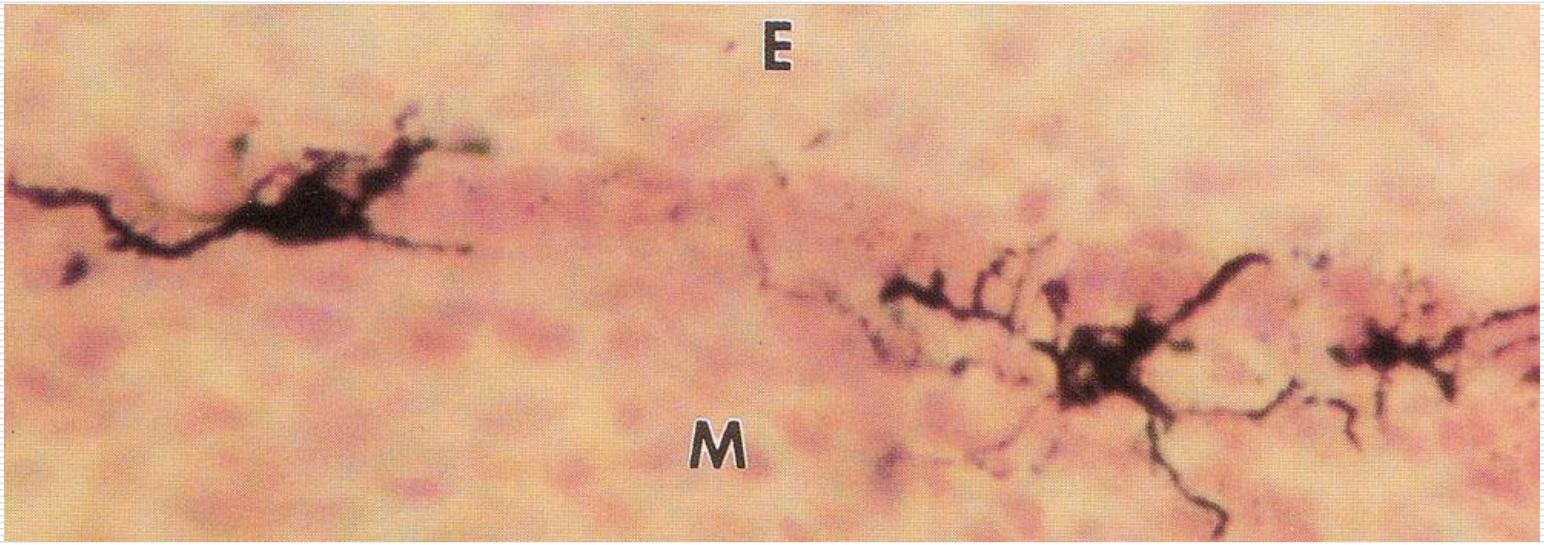
Skin color & Depigmenting agents



- Primary determinant of skin color: amount and type of melanin.

- Synthesis of melanin occurs in discrete organelles called melanosomes that are synthesized by melanocytes and subsequently transferred to and processed by keratinocytes in the epidermis.

Dendritic melanocytes



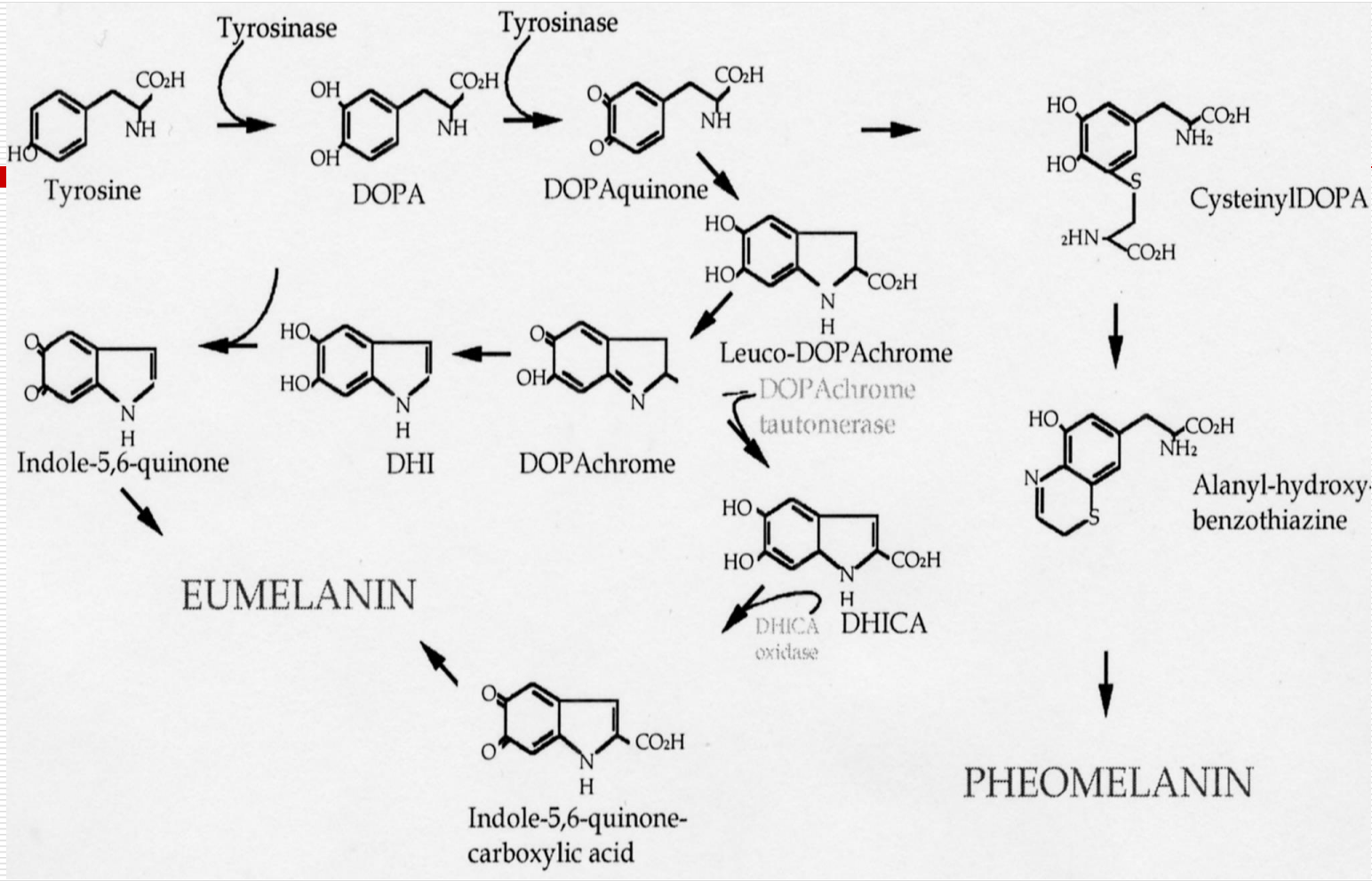
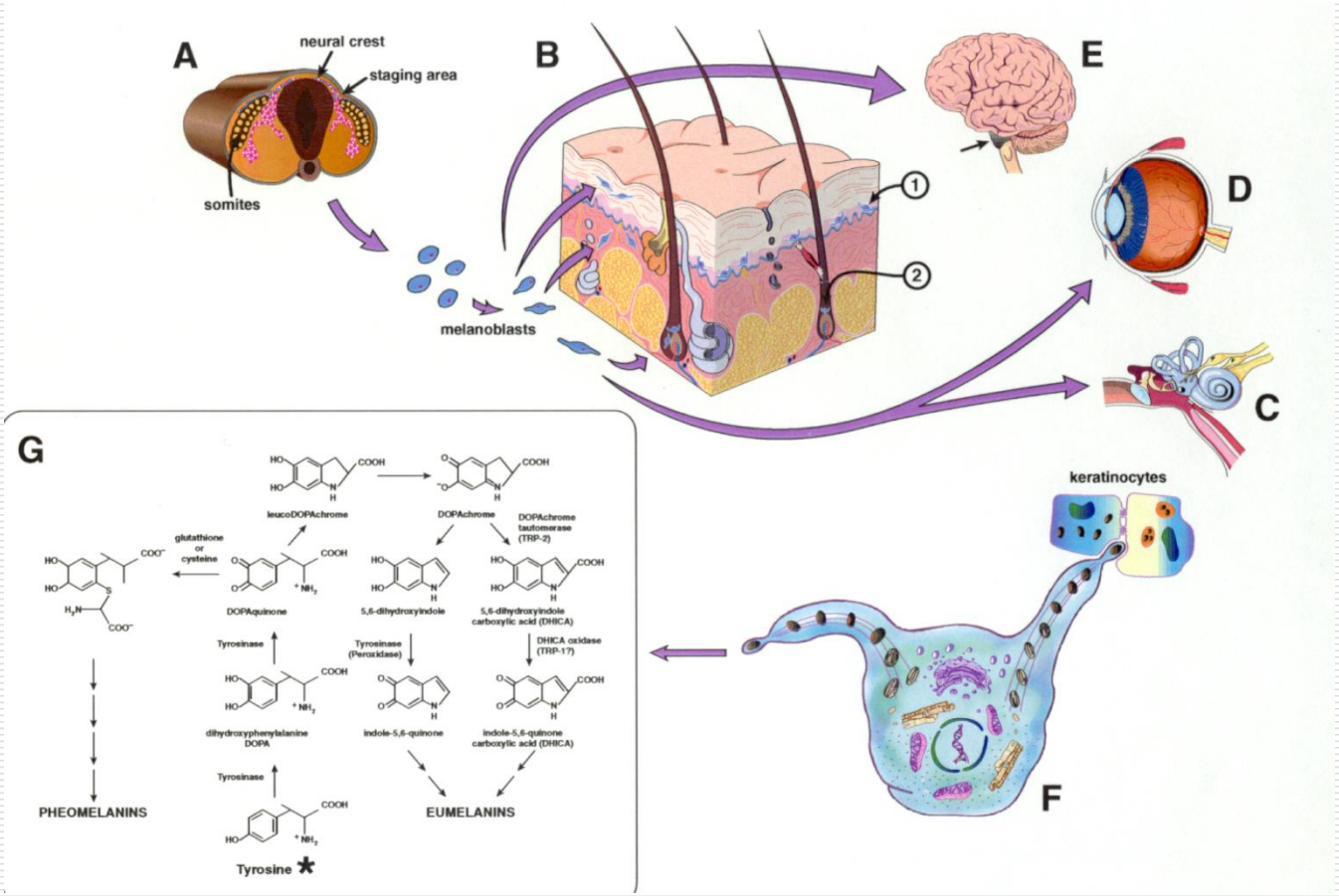


Figure 2. A modified representation of the Raper-Mason pathway *(King et al., 1995)*

- Synthesis of melanin begins with the amino acid tyrosine
- Tyrosinase is the rate limiting enzyme for melanin biosynthesis
- Tyrosinase catalyses the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and the subsequent oxidation of DOPA to DOPAquinone

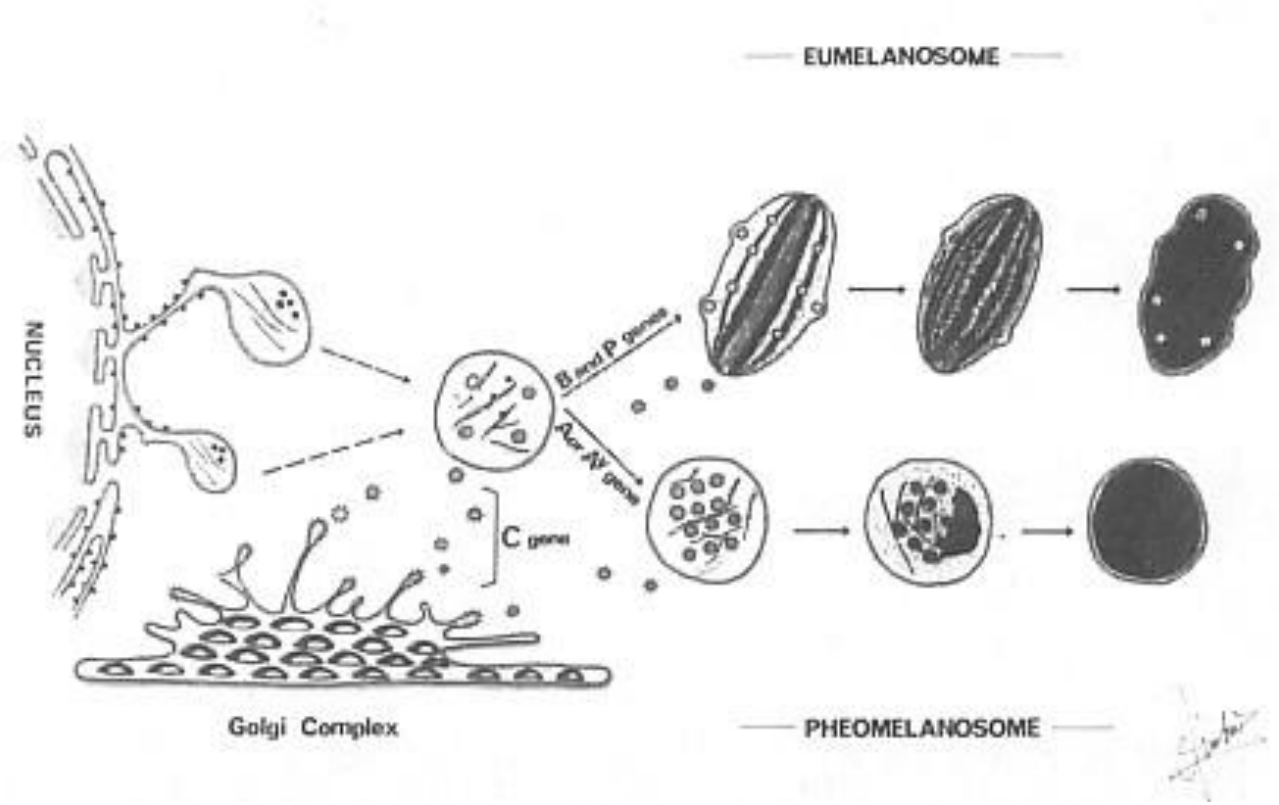
- Melanin pigmentation is due to two main groups of pigments
- The black to dark brown, insoluble eumelanins, and the alkali soluble pheomelanins, ranging from yellow to reddish brown
- The eumelanin production proceeds through the intermediates leucodopachrome to DOPAchrome


A
neural crest
staging area
somites
B
melanoblasts
1
2
E
D
C
keratinocytes
F
G
leucoDOPAchrome
DOPAchrome
DOPAchrome tautomerase (TRP-2)
glutathione or cysteine
DOPAquinone
5,6-dihydroxyindole
5,6-dihydroxyindole carboxylic acid (DHICA)
Tyrosinase
Tyrosinase (Peroxidase)
DHICA oxidase (TRP-17)
dihydroxyphenylalanine DOPA
indole-5,6-quinone
indole-5,6-quinone carboxylic acid (DHICA)
Tyrosinase
PHEOMELANINS
EUMELANINS
Tyrosine *

Two types of melanosomes

- Eumelanosomes are brown-black and oval shaped.
- Pheomelanosomes are reddish and round.
- Pheomelanosomes are formed through condensation with cysteine or glutathione.

Melanosomes are complex organelles formed on the Golgi Apparatus



- In darker-pigmented individuals:
- Melanocytes produce more melanin
- The melanosomes larger and more heavily melanized
- Melanosomes undergo degradation at a slower rate

(Szabo et al: Racial differences in the fate of melanosomes in human epidermis. Nature, 222: 1081, 1969)

Ultraviolet light and skin color

- Melanogenesis or “tanning” occurs when skin is exposed to UV light
- Skin’s major defense against further UV damage
- Increased melanin production and enhanced melanosome transfer

Sun exposure may lead to immediate pigment darkening (IPD) followed by delayed tanning. The table compares effects of both on melanocytes

Comparing Delayed Tanning and Immediate pigment darkening

Process	Immediate Tan (UVA and visible)	Delayed Tan (UVA and UVB)
Onset	Instantaneous, during exposure; fades immediately	Gradual, beginning at 48–72 h; lasts for weeks
Sunlight	UVA (320–380 nm), much less by UVB	UVB (290–320 nm), less by UVA (320–390 nm)
Melanogenesis		
Melanocyte	No numerical increase	Numerical increase by multiple exposure
Melanin	Photooxidation of pre-formed melanin	Synthesis of new melanin
Tyrosinase	No increased activity	Markedly increased activity
Melanosome	No new synthesis; ? increase in transfer to keratinocytes	New synthesis; increase in transfer to keratinocytes

- Excessive production and accumulation of melanins characterize a large number of skin diseases, which include acquired hyperpigmentation, such as melasma, solar lentigo and post-inflammatory hyperpigmentation.

- Such hyperpigmentary diseases, especially when they occur in the head and the neck, frequently result in loss of confidence and self esteem of the affected person.

Nordlund JJ, Boissy RE, Hearing VJ, King RA, Ortonne JP. The pigmentary system: physiology and pathophysiology. New York: Oxford University Press, 1998. Ortonne, J.P., Nordlund, J.J.: Mechanisms that cause abnormal skin color. New York, Oxford University Press, 1998

Acquired hyperpigmentation

Skin diseases and conditions

- Melasma
- Riehl's melanosis
- Poikiloderma of Civatte
- Erythromelanosis follicularis
- Linea fusca
- Post inflammatory hyperpigmentation

Exogenous causes

Ultraviolet exposure (e.g. melasma, solar lentigines, ephelides)

Photosensitizing agents (e.g. berloque dermatitis due to bergamot oil, furocoumarines)

Drugs (e.g. estrogens, tetracyclines, amiodarone, phenytoin, phenothiazines, sulfonamides)

Cosmetics

Other causes

Pregnancy

Liver disease

Addison's disease

Hemochromatosis

Pituitary tumors

Box 15.1 Acquired hyperpigmentation

Melasma

- Cholasma or " mask of pregnancy"
- Very difficult to treat
- Presents as irregular shaped blotches of light to dark brown pigmentation
- Usually seen on the upper lip, nose, cheeks, chin, forehead, and sometimes the neck
- Most commonly seen in the areas that receive sun exposure

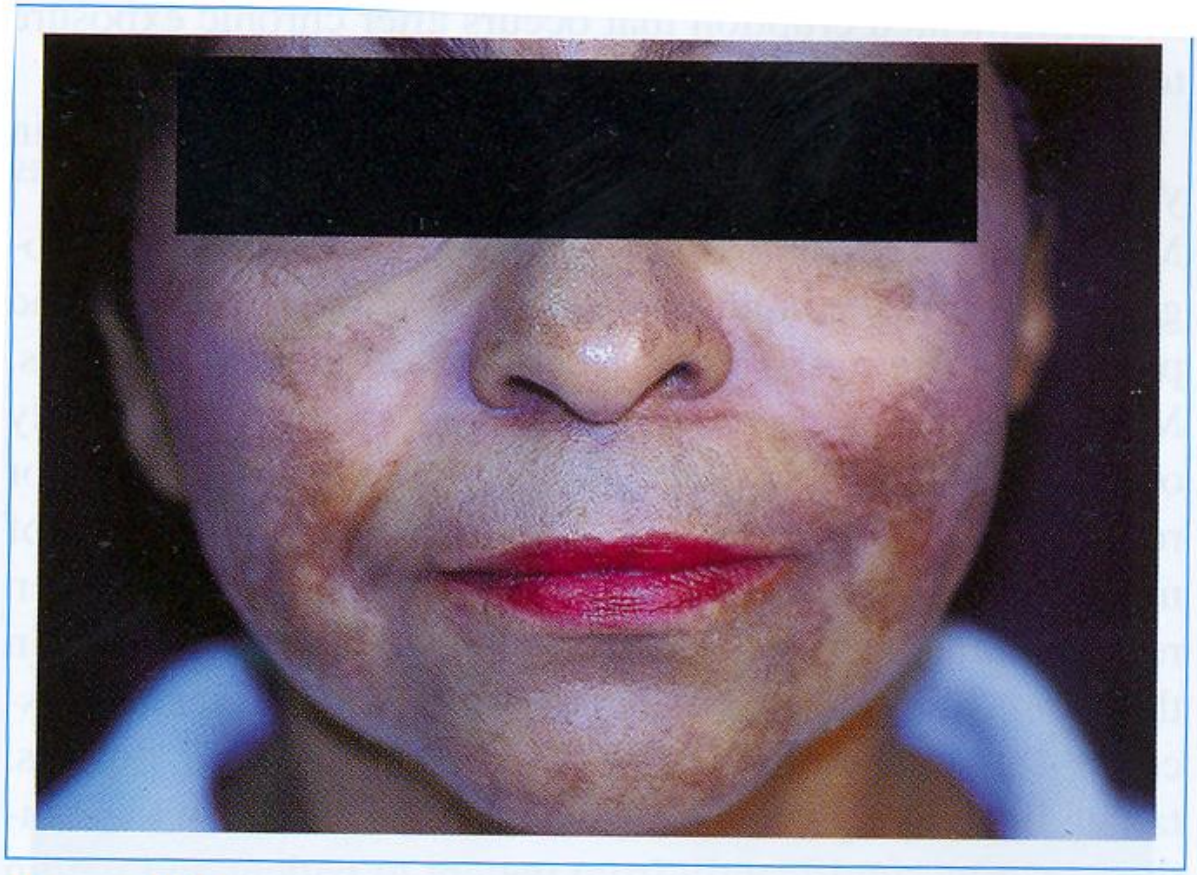
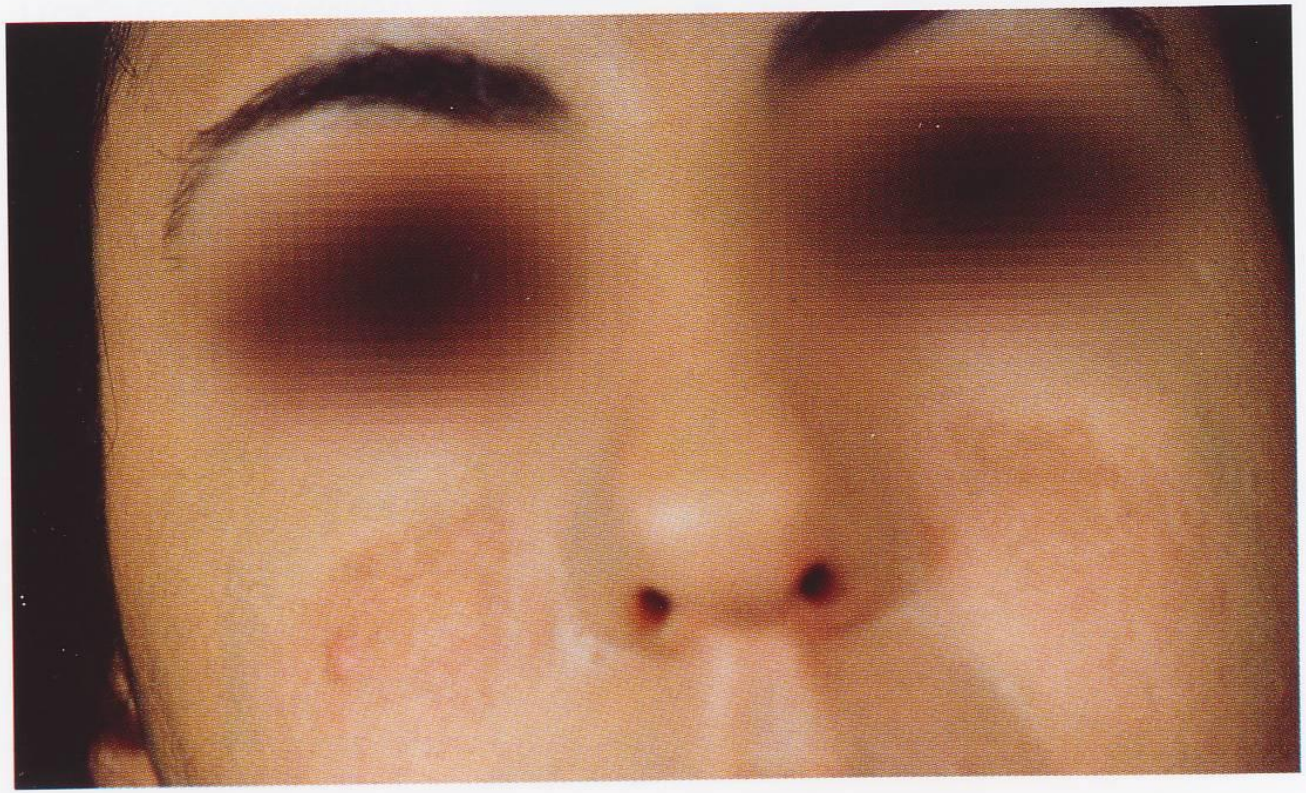


Figure 10-2.
Patient with diffuse melasma. The patient has not improved despite multiple therapies including depigmenting agents, chemical peels, and good sun protection.



Melasma.

Regimen for Patients with Melasma

Morning

1. Wash with an α-hydroxy acid-containing cleanser.
2. Apply a product with a combination of hydroquinone and kojic acid.
3. Apply a UVA/UVB sunscreen.
4. Wear a hat and avoid sun when possible.

Evening

1. Wash with an α-hydroxyacid-containing cleanser.
2. Apply a retinoid such as Retin-A™, Renova™, Differin™, Tazarac™, or Alustra™.

Undergo an in-office peel every two weeks (i.e., Jessner's, glycolic, or salicylic acid). Slowly increase peel strength as tolerated.

NOTE: Some patients develop exogenous ochronosis, or increased pigmentation, on exposure to hydroquinone. A good history should be taken, and if the patient is sensitive to hydroquinone, it should be avoided. Azelaic acid (Azelex™) is another option that is useful in all patients, but especially in those patients who cannot tolerate hydroquinone.

Melasma

- Seen most often during pregnancy or oral contraceptive use
- Melasma may diminish in the months following pregnancy or after discontinuing OC, the condition often persists, taking up to five years to resolve
- More common in women of darker skin types
- Estrogen and UV light are major contributing factors
- Other factors include: genetic predisposition, nutritional deficiency, and other hormone such as progesterone
- Antiepilepsy drugs (Hydantoin and Dilantin)
- Many women develop melasma on the upper lip after hot wax has been used to remove hair
- Melasma also occurs in men (mostly Middle Eastern or Asian)

http://dermnetnz.org/colour/melasma.html

What causes melasma?

The cause of melasma is complex. The pigmentation is due to overproduction of melanin by the pigment cells, melanocytes, which is taken up by the keratinocytes (epidermal melanosis) and/or deposited in the dermis (dermal melanosis). There is a genetic predisposition to melasma, with at least one-third of patients reporting other family members to be affected. In most people melasma is a chronic disorder.

Known triggers for melisma include:

- Sun exposure—this is the most important avoidable risk factor
- Pregnancy—in affected women, the pigment often fades a few months after delivery
- Hormone treatments—oral contraceptive pills containing oestrogen and/or progesterone, hormone replacement, intrauterine devices and implants are a factor in about a quarter of affected women
- Certain medications, scented or deodorant soaps, toiletries and cosmetics—these may cause a phototoxic reaction that triggers melasma, which may then persist long term
- Hypothyroidism (low levels of circulating thyroid hormone)

WebMD Archive

Pregnancy Mask and Other Pigment Problems

While there is no specific treatment for pregnancy pigmentation problems, staying out of the sun can definitely diminish the amount of discoloration you experience, so can wearing a sunscreen anytime you are outdoors.

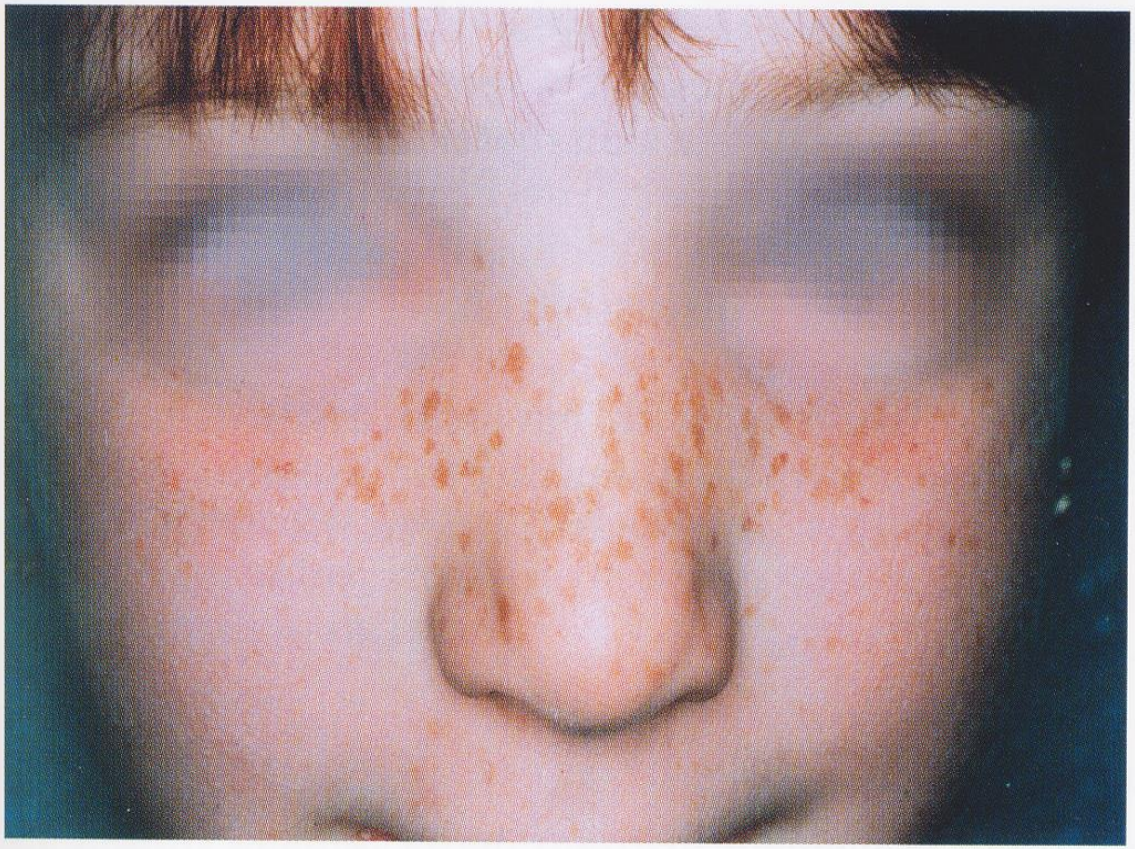
While the jury is still out on the safety of traditional skin-lightening ingredients such as hydroquinone during pregnancy, Jamal says there are others with an established safety profile you can safely try.

"You can use azelaic acid, which is good for pigment, as well as any topical vitamin C product, which helps suppress pigment naturally," she says.

http://www.webmd.com/baby/features/pregnancy-skin-care-get-that-glow?page=2

Freckles

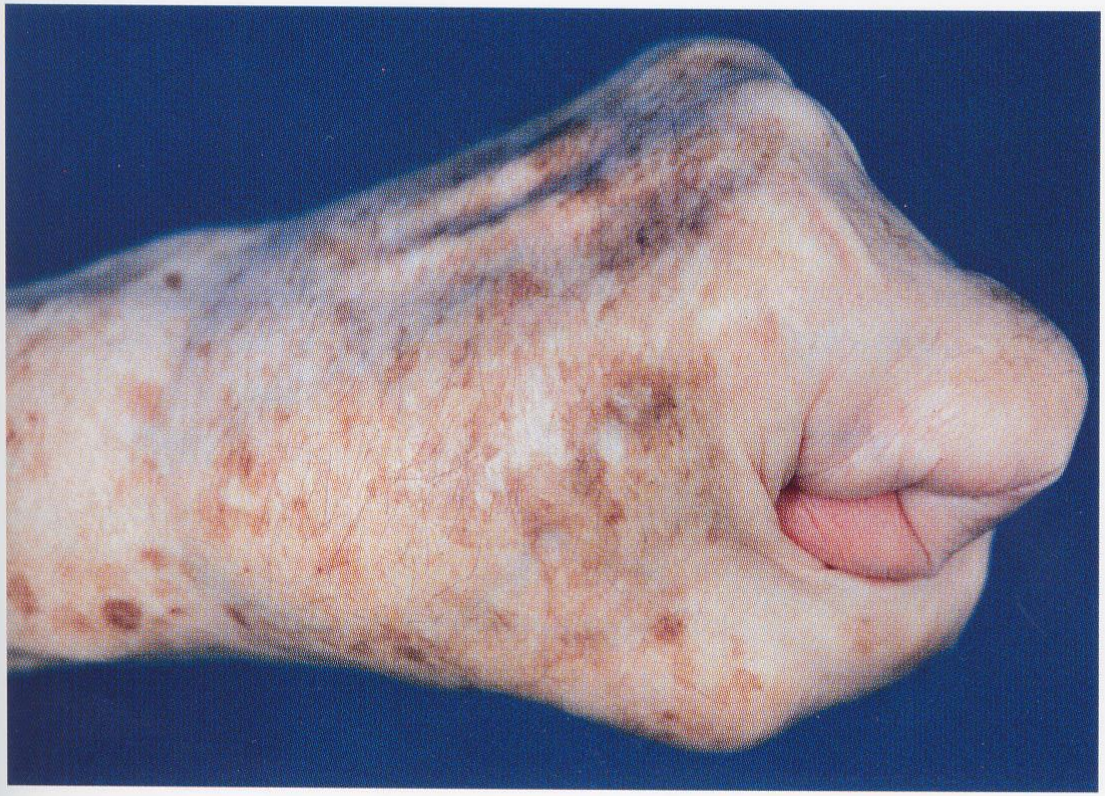
- Small pale-brown spots, usually found in light-skinned individual with light hair or red hair
- Appears in early childhood between the ages of two and four years
- Commonly occur in areas of skin exposed to the sun (face, shoulders, and the upper back)
- In the summer they become darker



Freckles.

Solar Lentigo

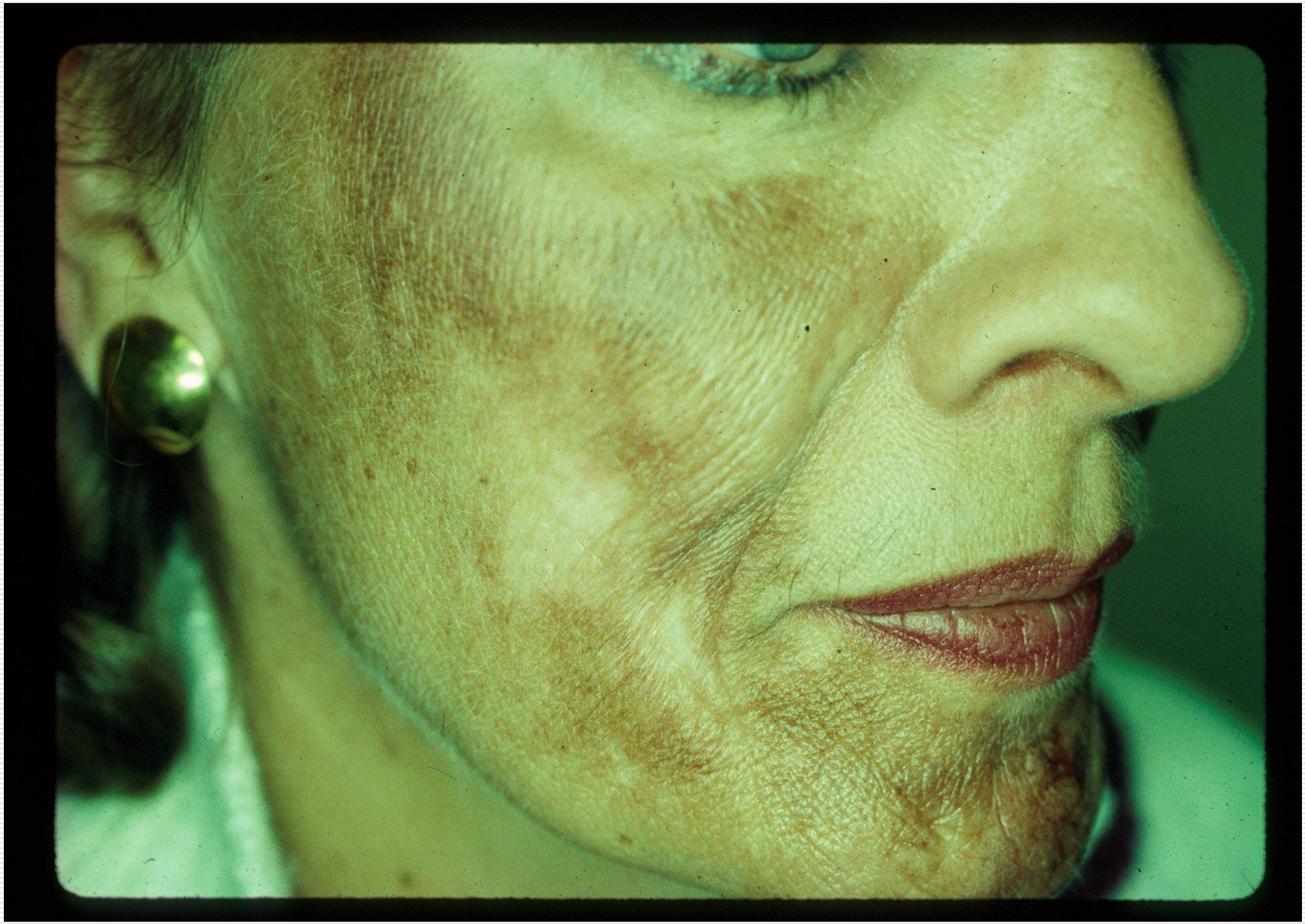
- Macular brown lesions usually 1 cm in diameter
- Sun rather than age is the causative factor
- Face and backs of hands
- Seldom seen among patients under 50→ “senile lentigos”



'Sun spots' on the back of the hand.

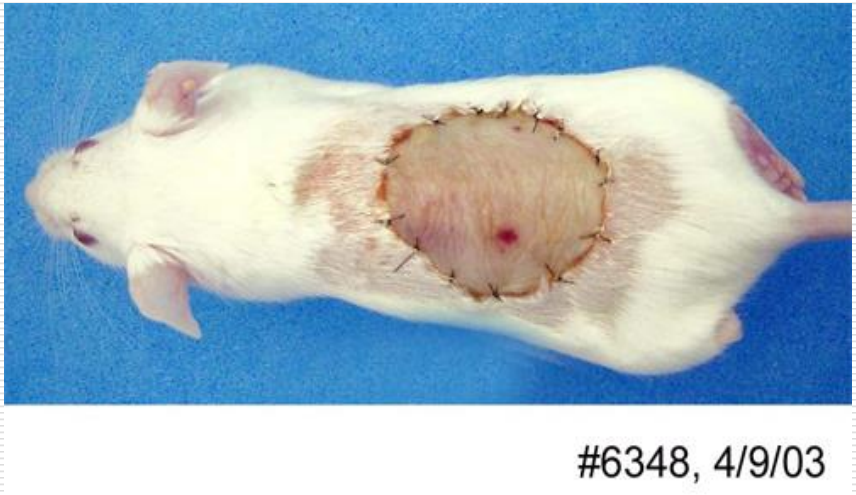
Postinflammatory Hyperpigmentation

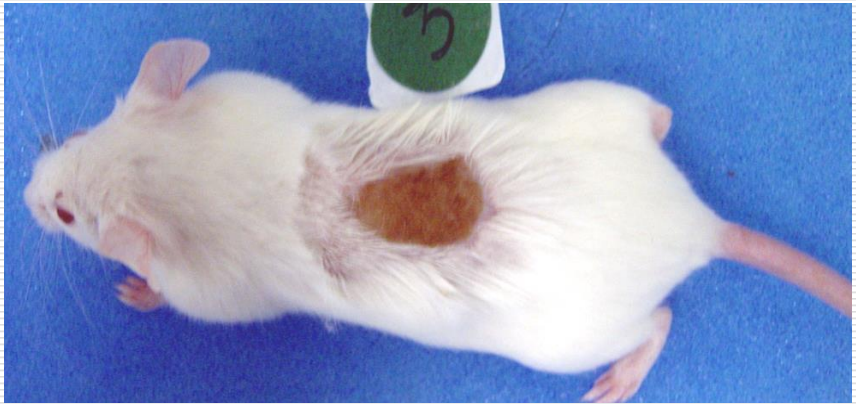
- Caused by variety of skin disorders
- Presents as irregular darkly pigmented spots arising in areas of previous inflammation
- It is a consequence of increased melanin synthesis in response to a cutaneous insult
- Mot frequently among patients with darker skin types
- Minor conditions such as acne, eczema, and allergic reactions can lead to PIHP
- In addition, burns, surgeries, and trauma, or treatments such as chemical peels and laser resurfacing can precipitate it



Hyperpigmentation of skin grafted on a burn patient that is a consequence of wound healing and postinflammatory processes

(Nordlund, J.J. and Z.A. Abdel-Malek, Mechanisms for postinflammatory hyperpigmentation and hypopigmentation. Prog Clin Biol Res, 1988. 256: p. 219-36)





7/1/03

Hyperpigmentation of human skin grafted to immunocompromised mice.

(Saja H. Hamed,** Penkanok Sriwiriyanont, Mitchell A. deLong, Marty O. Visscher, R. Randall Wickett, Raymond E. Boissy. Comparative efficacy and safety of deoxyarbutin, a new tyrosinase-inhibiting agent. J Cosmet Sci., 57(4): 291-308, **2006)

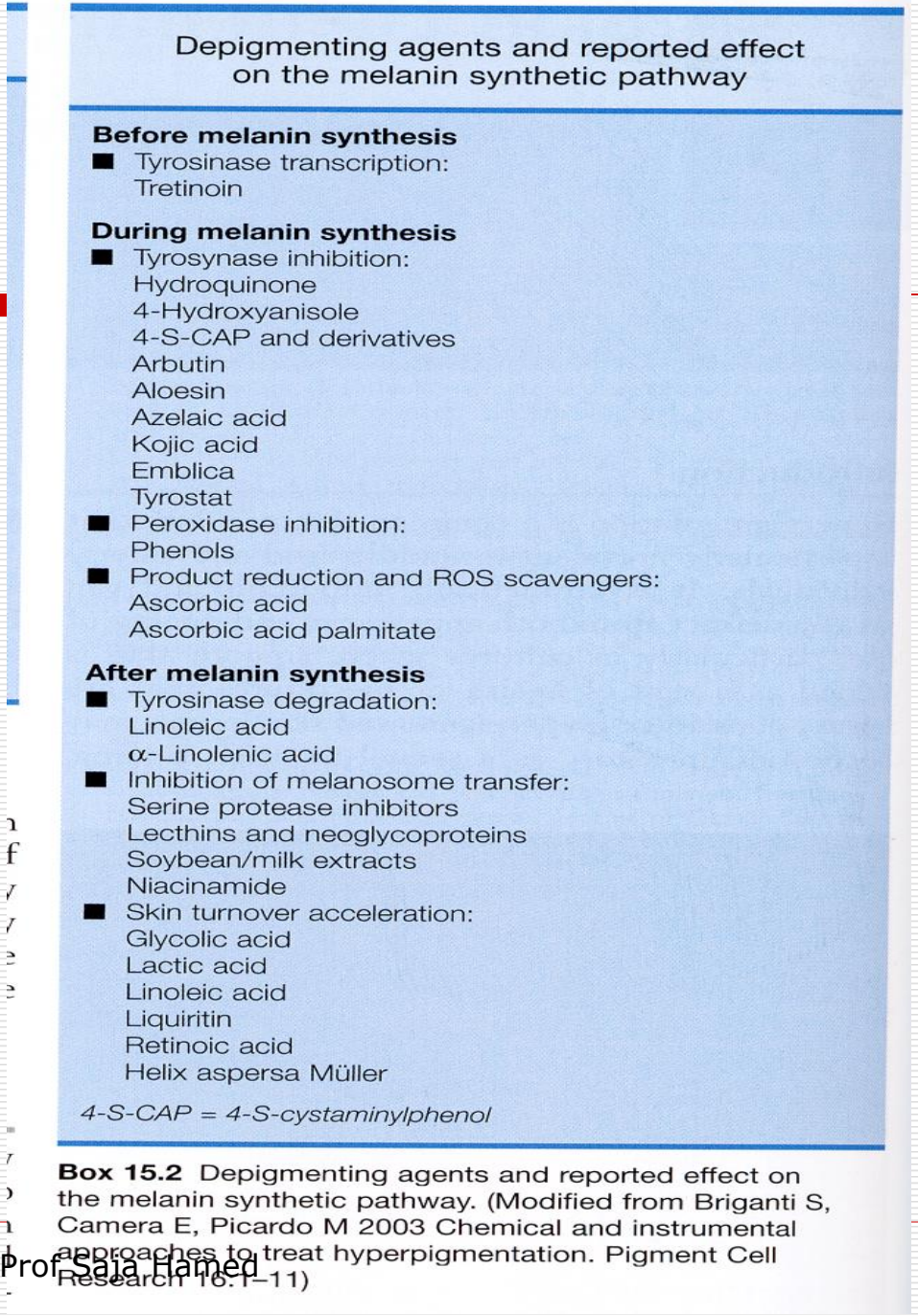
Postinflammatory Hyperpigmentation

- Difficult to treat because it occurs in individuals susceptible to hyperpigmentation following inflammation (but resolve better than melasma)
- Further inflammation, **as induced by peels or lasers**, would worsen the process
- Only nonirritating topical products are potentially useful to treat this condition (e.g. kojic acid, retinoids)
- Best treatment approach is sun avoidance, sunscreen use, and patience because these lesions tend to improve with time

Postinflammatory Hyperpigmentation

- Very important to avoid irritating cosmetics, harsh scrubs, excessive peelings..etc
- Complete holiday from all of your makeup will help (one of those could be the problem)

Depigmenting Agents



Depigmenting agents and reported effect on the melanin synthetic pathway

Before melanin synthesis

- Tyrosinase transcription:
  - Tretinoin

During melanin synthesis

- Tyrosynase inhibition:
  - Hydroquinone
  - 4-Hydroxyanisole
  - 4-S-CAP and derivatives
  - Arbutin
  - Aloesin
  - Azelaic acid
  - Kojic acid
  - Emblica
  - Tyrostat
- Peroxidase inhibition:
  - Phenols
- Product reduction and ROS scavengers:
  - Ascorbic acid
  - Ascorbic acid palmitate

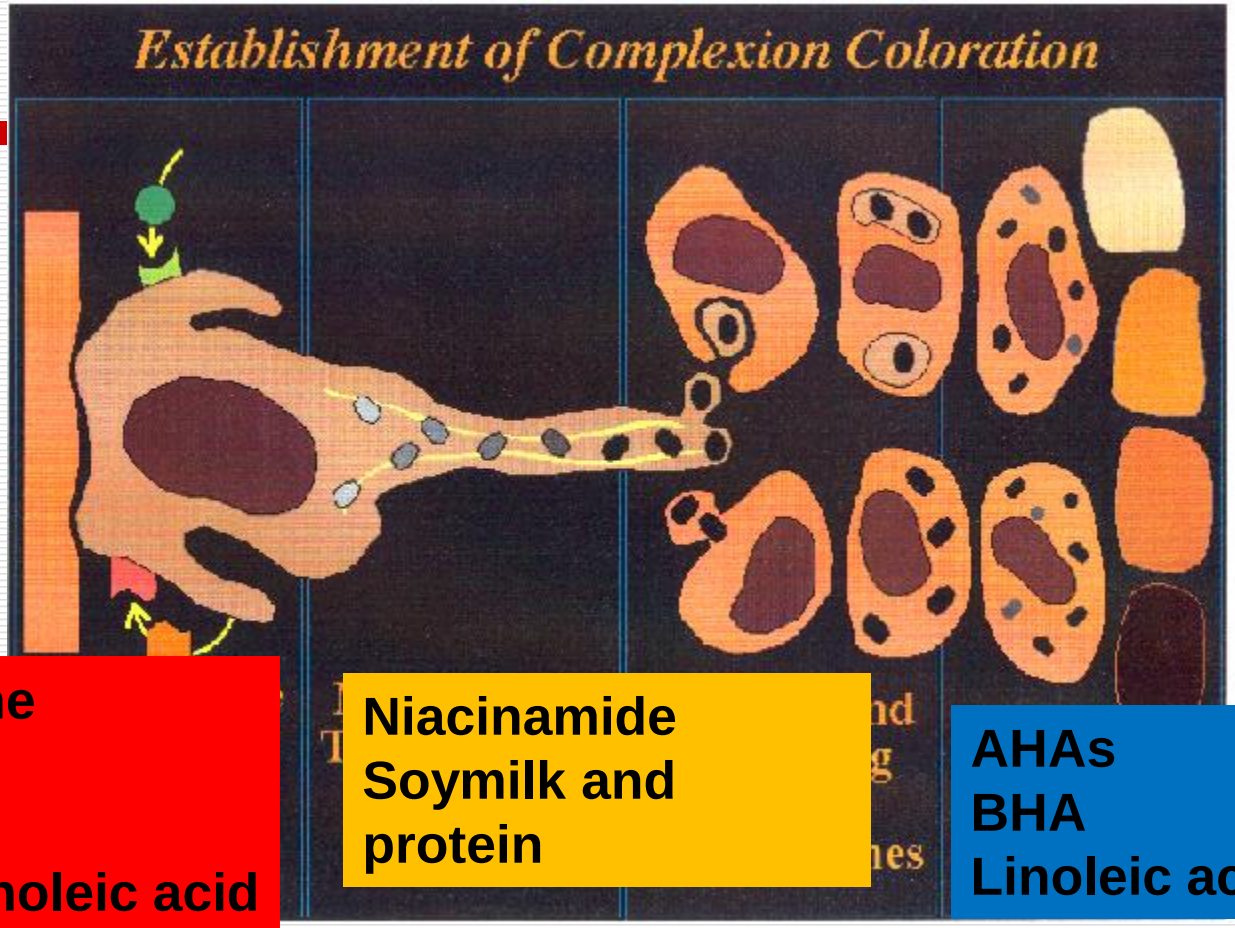
After melanin synthesis

- Tyrosinase degradation:
  - Linoleic acid
  - α-Linolenic acid
- Inhibition of melanosome transfer:
  - Serine protease inhibitors
  - Lecthins and neoglycoproteins
  - Soybean/milk extracts
  - Niacinamide
- Skin turnover acceleration:
  - Glycolic acid
  - Lactic acid
  - Linoleic acid
  - Liquiritin
  - Retinoic acid
  - Helix aspersa Müller

4-S-CAP = 4-S-cystaminylphenol

Box 15.2 Depigmenting agents and reported effect on the melanin synthetic pathway. (Modified from Briganti S, Camera E, Picardo M 2003 Chemical and instrumental approaches to treat hyperpigmentation. Pigment Cell Research 16:1–11)

Main strategies for depigmentation



Hydroquinone
Kojic Acid
Arbutin
Oleic acid, linoleic acid and or α-linolenic acid
Licorice extract
Aloesin
Antioxidants (C&E)
Azelaic Acid

Niacinamide
Soymilk and protein

AHAs
BHA
Linoleic acid

Retinoids

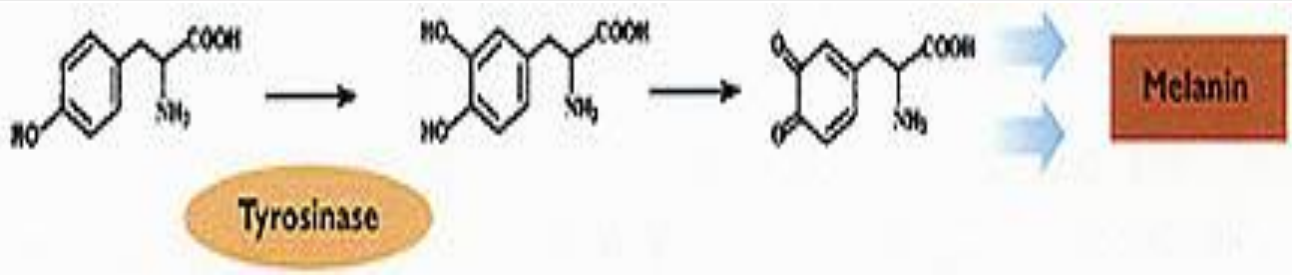
Depigmenting Agents

- Although there are many products available, the number of effective agents to treat hyerpigmentation disorders is relatively small

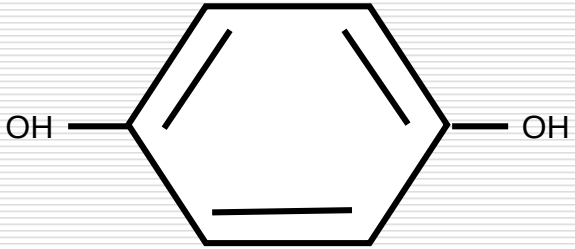
- Most of these agents require months of use for improvement to be seen

Tyrosinase Inhibitors

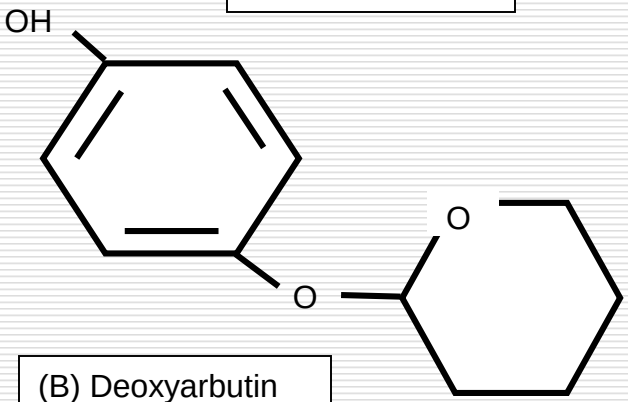
- Binding of an inhibitor to the active site of tyrosinase results in decreased melanin formation.



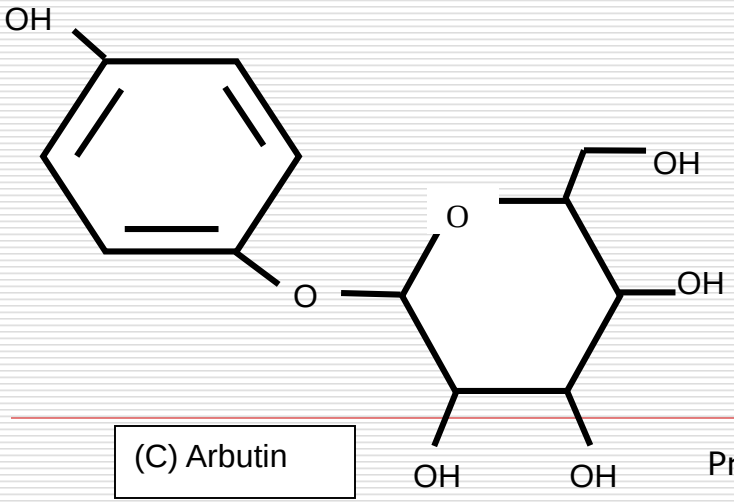
- Hydroquinone, kojic acid, and arbutin are competitive inhibitors of tyrosinase that are currently being used in drugs to ameliorate hyperpigmented lesions and in cosmetics to lighten skin complexion.



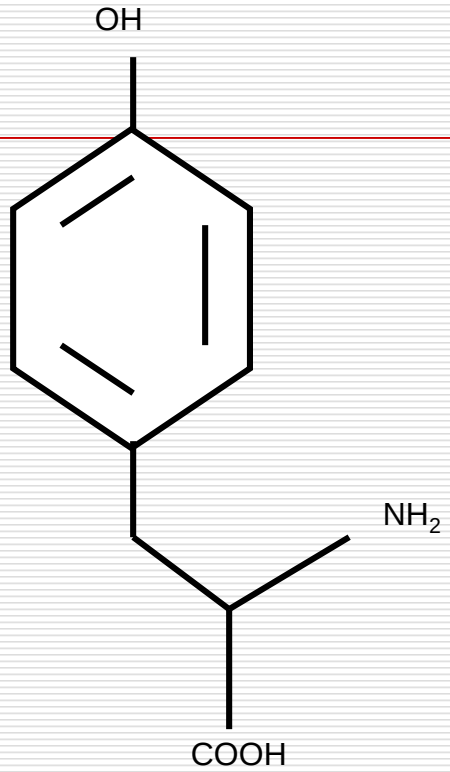
(A) Hydroquinone



(B) Deoxyarbutin



(C) Arbutin



(D) Tyrosine

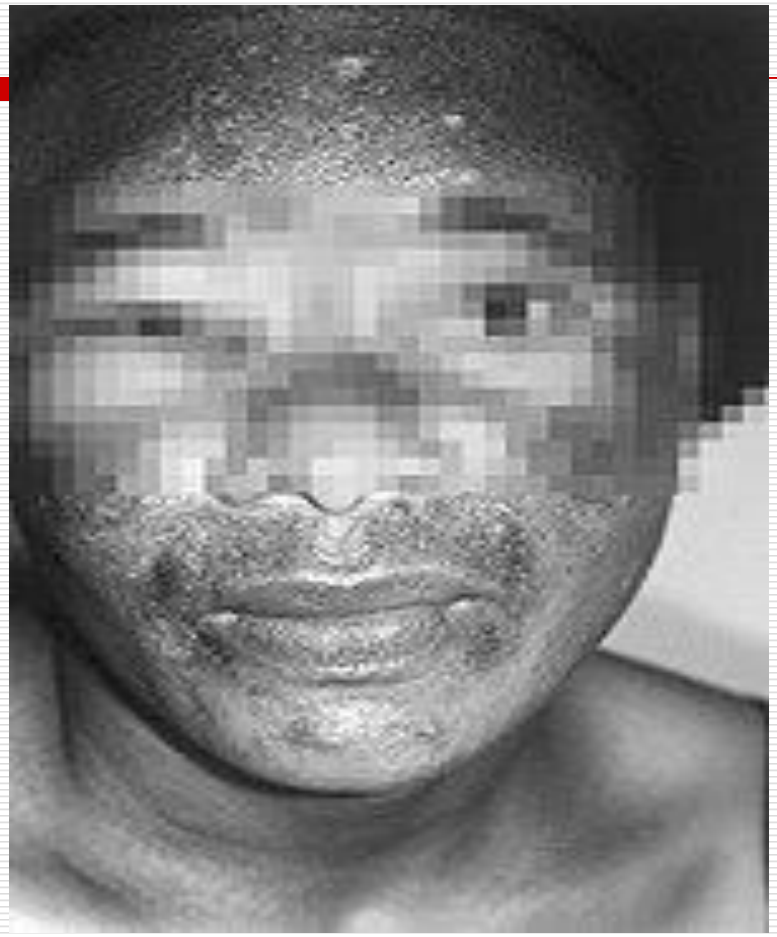
Prof Saja Hamed

Tyrosinase inhibitors:
a. Hydroquinone

- Used in OTC and prescription drugs as a skin lightening agents
- Occurs naturally in many plants as well as in coffee, tea, beer, and wine
- It exerts its depigmenting effect by inhibiting tyrosinase
- Available OTC in 2% concentrations and by prescription in 4% concentration
- 4% concentration is more irritating and more likely to cause side effects
- Due to safety concerns (potential mutagenic properties), its use has been banned as cosmetic depigmenting agents in European Union and Japan and is highly regulated in Asia

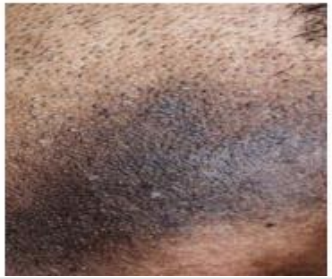
Tyrosinase inhibitors:
a. Hydroquinone

- Several new combination agents are now available: a prescription drug containing 4% HQ, tretinoin and low potency fluorinated steroid is available for melasma treatment
- Topical use of HQ may lead to exogenous ochronosis
- It is asymptomatic blue-black macules in the area of HQ application that occur after prolonged use of HQ and difficult to reverse
- Occur more commonly among patients with darker skin types
- It is advisable to use it in four-month cycles only, alternating it with kojic acid, azelaic acid, and other depigmenting agents
- Just use it on affected area/spot
- Not o be used in pregnant women
- Contact with the nails should be avoided while using hydroquinone
- One may notice irritation of the skin following HQ use manifested by an itching sensation and redness



Prolonged HQ usage may lead to untoward effects like

exogenous ochronosis.



Tyrosinase inhibitors:
a. Hydroquinone

- HQ oxidation to highly reactive toxic quinone, either by tyrosinase interaction or through spontaneous oxidation, is believed to be participating in toxic degradation of melanocytes, including the melanogenic apparatus.

- Reactive quinones are thought to indiscriminately bind and damage lipids, proteins, and nucleic acid.
- Be careful: if a cream contain hydroquinone turned its color to light brown → stop using it
- *Passi, S., Nazzaro-Porro, M., 1981. Penney K.B., Smith C.J., Allen, J.C., 1984. Palumbo, A., d'Ischia, M., Misuraca, G., Prota, G., 1992. Briganti, S., Camera, E., Picardo, M., 2003*

Tyrosinase inhibitors: b. Bearberry and Arbutin

- *Arctostaphylos uva ursi* (the bear's grape)
- Arbutin (hydroquinone-beta-D-glucopyranoside) is the main constituents
- Consists of a molecule of HQ bound to glucose
- Its effectiveness is questionable

2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Alpha-arbutin (α-arbutin) (INCI name: Alpha-Arbutin, Chemical name: 4-Hydroxyphenyl-alpha-D-glucopyranoside, CAS No. 84380-01-8, EC No. 617-561-8) and the structurally related compound (optical isomer) beta-arbutin (β-arbutin) (INCI Name: Arbutin, Chemical name: 4-Hydroxyphenyl-b-D-glucopyranoside**,** CAS No. 497-76-7, EC No. 207-850-3) are similar cosmetic ingredients currently not regulated under the Cosmetic Regulation (EC) No. 1223/2009. Among the reported functions for both α- and β-arbutin are antioxidant, skin bleaching and skin conditioning.

The safety of α- and β-arbutin has been previously assessed in the SCCS/1552/15[1 2 3] and SCCS/1550/15, respectively. The effects of arbutins on the skin could be attributed to their gradual hydrolysis and release of hydroquinone (HQ). Hydroquinone (CAS No. 123-31-9. EC No. 204-617-8) is listed in entry 1339 of Annex II to the Cosmetic Regulation, which means that it is prohibited as cosmetic ingredient with the exception of entry 14 in Annex III (restricting its use to professionals in artificial nail systems with a maximum concentration up to 0.02% in the finished product).

In the relevant SCCS Opinions (SCCS/1552/15 and SCCS/1550/15), the SCCS concluded that

1. the use of α-arbutin is safe for consumers in cosmetic products in a concentration up to 2% in face creams and up to 0.5 % in body lotions.

2. the use of β-arbutin is safe for consumers in cosmetic products in a concentration up to 7% in face creams provided that the contamination of hydroquinone in the cosmetic formulations remains below 1 ppm.

Nevertheless, the SCCS highlighted in both Opinions that a potential combined use of hydroquinone releasing substances in cosmetic products has not been evaluated.

Tyrosinase inhibitors: d. Kojic acid

- Is a fungal metabolite commonly produced by many species of *Aspergillus, Acetobacter, and Penicillium*
- Widely used as a food additive for preventing enzymatic browning and to promote reddening of unripe strawberries
- Used in concentrations between 1 and 4% and is often more effective in combination with other ingredients

Tyrosinase inhibitors:
d. Kojic acid

- Products that contain kojic acid are used twice a day for one to two months
- Unfortunately, it is associated with contact allergy and is considered to have high sensitizing potential
- A 1% concentration is usually used

Tyrosinase inhibitors: e. Licorice extract

- Licorice extract is obtained from the root of *Glycyrrhiza glabra linneva*
- Its main active ingredient is 10-40% glabridin
- Inhibit tyrosinase activity
- It also demonstrated anti-inflammatory effects *in vitro*

Other Agents:
f. Aloesin

- A natural compound that is isolated from Aloe vera
- Inhibits tyrosinase at non-cytotoxic concentrations

Table 1. Some depigmenting lightening agents and their mushroom tyrosinase inhibition activities from natural sources

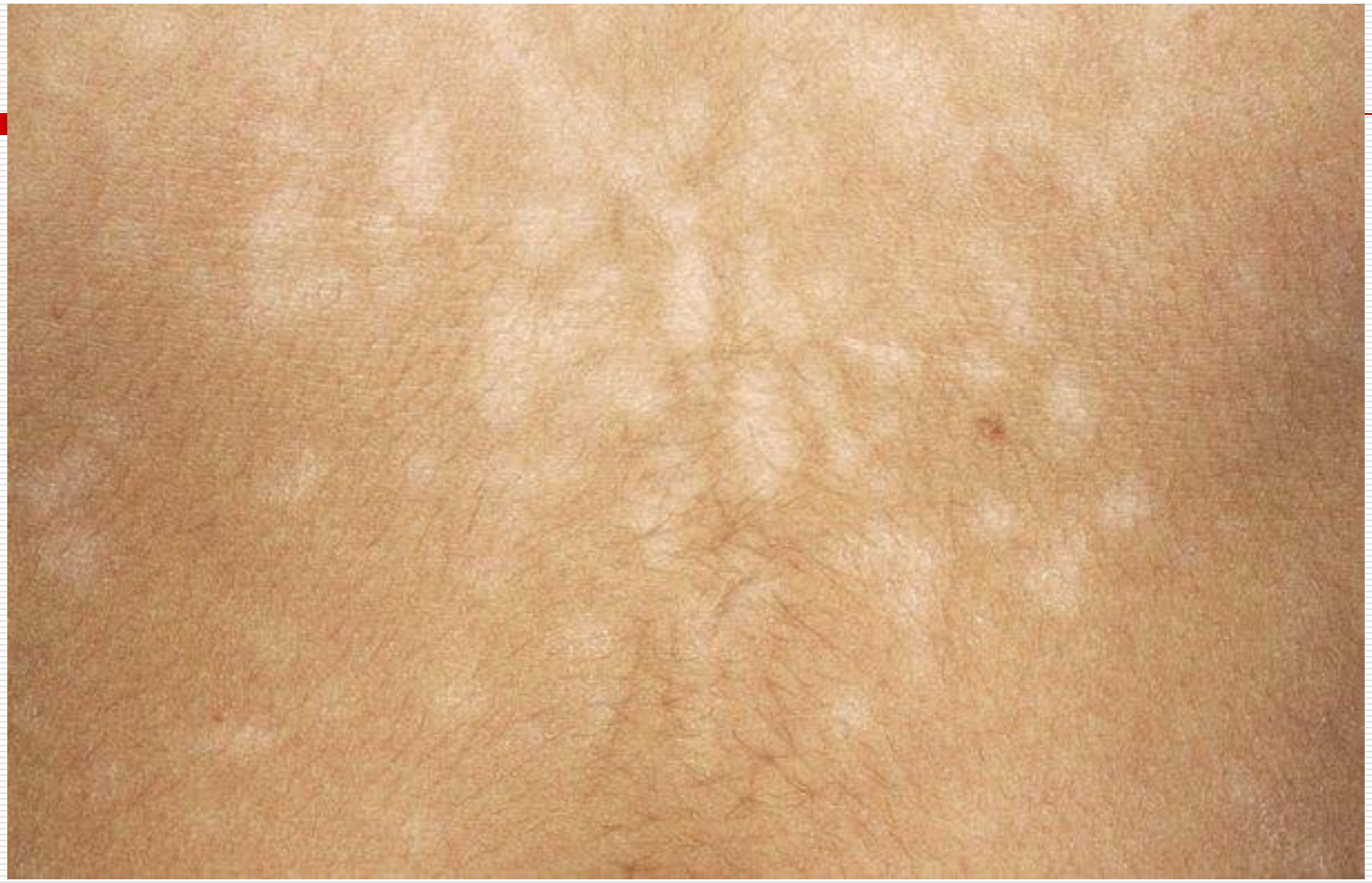
Inhibitor	Source	Botanical name	Type of inhibition	IC_{50} (mM)	Reference
Arbutin	*Gvae grsi*	*Arctostaphylos uva-ursi*	Competitive Uncompetitive	0.04	Yagi *et al.*, 1987
Aloesin	*Aloe vera*	*Aloe barbadensis*	Noncompetitive	0.1	Yagi *et al.*, 1987
Anacardic acid	*Anacardium occidentale*	*Anacardium occidentale*	Competitive	0.0001	Kubo *et al.*, 1994
Anisic acid	Anise oil	*Pimpinella anisum*	Uncompetitive	0.68	Lee, 2002
Agaritine	*Agaricus bisporus*	*Agaricus bisporus*	Uncompetitive	0.03	Espin and Jolivet, 1998
Anisaldehyde	Anise oil	*Pimpinella anisum*	Noncompetitive	0.38	Lee, 2002
Cumic acid	Cumin seed	*Cuminum cyminum*	Noncompetitive	0.26	Kubo and Kinst-Hori, 1988
Cuminaldehyde	Cumin seed	*Cuminum cyminum*	Noncompetitive	0.05	Kubo and Kinst-Hori, 1988
p-Coumaric acid	Ginseng Radix	*Panax ginseng*	Mixed	3.65	Lim *et al.*, 1991
ECG	Green tea	*Thea chinensis*	Competitive	0.035	No *et al.*, 1999
EGCG	Green tea	*Thea chinensis*	Competitive	0.034	No *et al.*, 1999
Ia	*Agaricus hortensis*	*Agaricus hortensis*	Competitive	0.03	Madhosingh and Sundberg, 1974
3,4-Dihydroxycinnamic acid	*Pulsatilla cernua*	*Pulsatilla cernua*	Noncompetitive	0.97	Lee, 2002
Oxyresveratrol	*Mori Cortex*	*Morus alba*	Noncompetitive	0.001	Lee, 2002
Kaempferol	Croci Stigma	*Crocus sativus*	Competitive	0.23	Kubo and Hori, 1999
Trans-cinnamaldehyde	Cinnamomi Cortex	*Cinnamomum cassia*	Competitive	0.85	Lee *et al.*, 2000
Ib		*Agaricus hortensis*	Noncompetitive	0.03	Madhosingh and Sundberg, 1974
4-Hydroxy-3-methoxycinnamic acid	Pulsatillae Radix	*Pulsatilla cernua*	Noncompetitive	0.97	Lee, 2002; Lee, *et al.*, 2000
9-Hydroxy-4-methoxypsoraln	Angelicae dahuricae Radix	*Angelica dahurica*	Noncompetitive	0.2	Piao *et al.*, 2004
5-hydroxymethyl-2-furfural	*Dictyophora indusiata*	*Dictyophora indusiata*	Noncompetitive	0.98	Sharma *et al.*, 2004

Melanocyte-Cytotoxic Agents
Azelaic acid:

- A naturally occurring acid
- Its depigmenting effect is most apparent in highly active melanocytes with minimal effects in normally pigmented skin
- Generally well tolerated and can be used for extended periods
- Transient erythema and cutaneous irritation characterized by scaling, itching which generally resolves after 2-4 weeks of application

Melanocyte-Cytotoxic Agents
Azelaic acid:

- Its main actions are likely due to its antiproliferative and cytotoxic effects
  (Fitton & Goa: Azelaic acid: a review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary disorders. Drugs 41: 780, 1991)
- it is an excellent alternative for patients who cannot tolerate hydroquinone
- 10%, 20%, and 35%
- Applied twice daily for several months
- Fungal infection of the skin called *pityriasis vesicolor*



Other Agents: α-Hydroxy and ß- Hydroxy Acids:

- Causes faster desquamation of the pigmented keratinocytes
- The removal of superficial layers of epidermis with glycolic acid peels can enhance the penetration of other topical skin lighteners such as hydroquinone

Other Agents: Niacinamide

- The amide form of vitamin B3
- Inhibit melanosome transfer
- Anti-inflammatory
- Water soluble
- More scientific evidence are needed to substantiate the overrated claims
- 1-3%

Review > Skin Pharmacol Physiol. 2014;27(6):311-5. doi: 10.1159/000359974. Epub 2014 Jun 27.

Niacinamide – mechanisms of action and its topical use in dermatology

Johannes Wohlrab [1], Daniela Kreft

Affiliations + expand

PMID: 24993939 DOI: 10.1159/000359974

Abstract

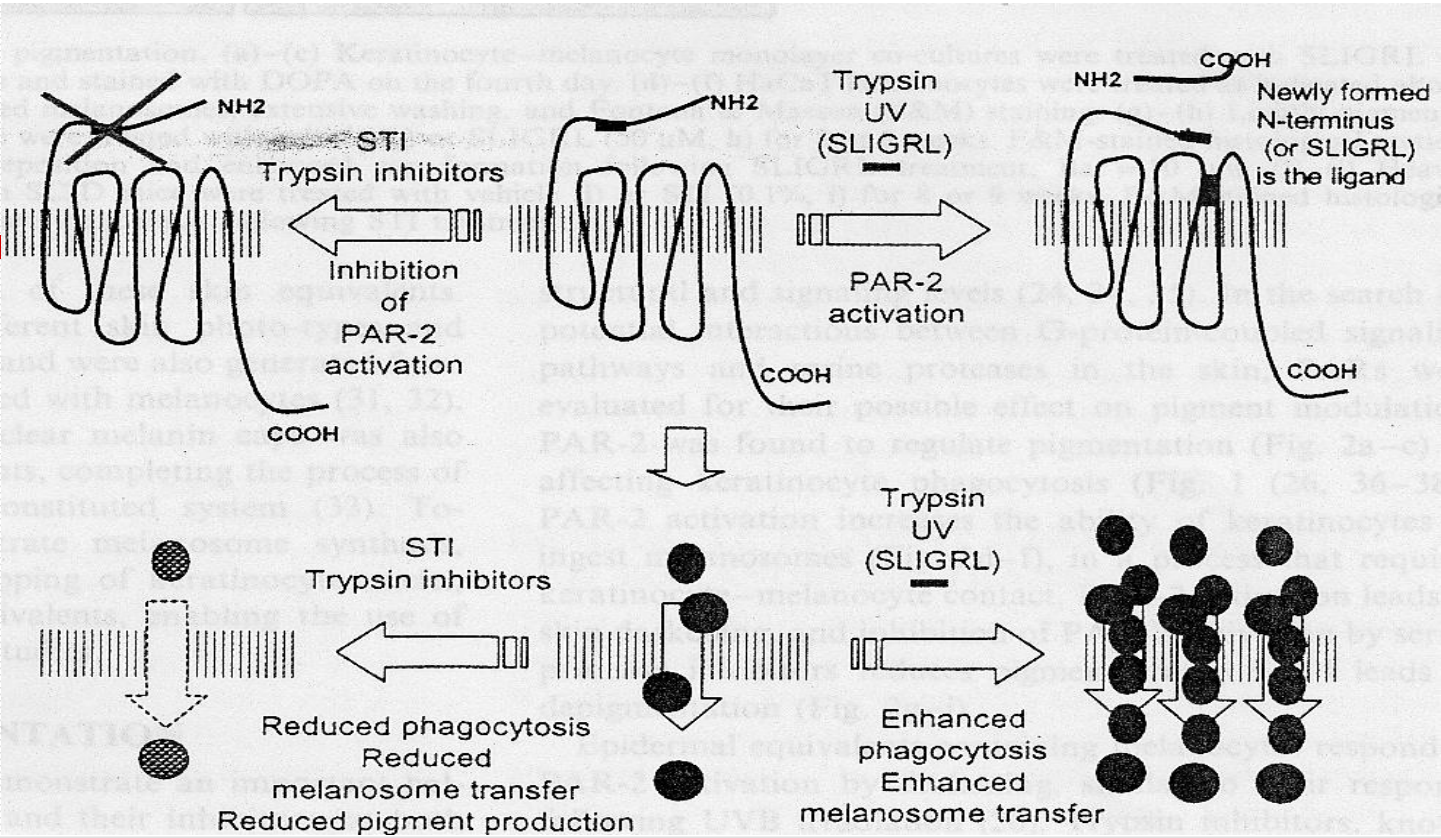
Niacinamide, an amide of vitamin B3 (niacin), is a hydrophilic endogenous substance. Its effects after epicutaneous application have long been described in the literature. Given a sufficient bioavailability, niacinamide has antipruritic, antimicrobial, vasoactive, photo-protective, sebostatic and lightening effects depending on its concentration. Within a complex metabolic system niacinamide controls the NFκB-mediated transcription of signalling molecules by inhibiting the nuclear poly (ADP-ribose) polymerase-1 (PARP-1). Niacinamide is a well-tolerated and safe substance often used in cosmetics. Clinical data for its therapeutic use in various dermatoses can increasingly be found in the literature. Although the existing data are not sufficient for a scientifically founded evaluation, it can be stated that the use of niacinamide in galenic preparations for epicutaneous application offers most interesting prospects.

Ingredient : NIACINAMIDE

INCI Name	NIACINAMIDE
Description	
CAS #	98-92-0
EC #	202-713-4
Cosmetics Regulation provisions	
Functions	• SMOOTHING
SCCS opinions	
Identified INGREDIENTS or substances e.g.	

Other Agents:
Soy

- Soymilk and soymilk- derived proteins are able to inhibits PAR-2 activation thus reduce melanosomes transfer
- Soybeans contain the small proteins Bowan-Birk inhibitor (BBI) and soybean trypsin inhibitor (STI)
- The effect is present only with fresh soy milk and not with pasteurized soy milk



A Schematic representation of PAR-2 activation and inhibition and the effects on keratinocyte phogocytosis and melanosome transfer *(Seiberg, M., 2001)*

Other Agents: Retinoids

- It is a frequent adjuvant in the treatment of pigmentary disorders
- Works at the transcription level of tyrosinase
- Retinoic acid inhibit induction of tyrosinase
- Also it accelerate epidermal turnover causing keratinocytes to be shed more quickly
- Alustra (0.3% retinol and 4% HQ)

Other Agents: Vitamin C

- Magnesium –L- ascorbyl-2-phosphate (VC-PMG)
- It interferes with pigment production at various oxidative steps of melanin synthesis by interacting with copper ions at the tyrosinase active site
- Antioxidant and depigmenting agent and it stimulate collagen synthesis

Kojic acid: irritant and allergic contact dermatitis

Azelaic acid: Just for hyperpigmentory disorders

Ascorbic acid (Vitamin C):

Well tolerated but highly unstable

AHA (glycolic and lactic acid): Increase skin sensitivity to sun

Gl

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Glutathione for skin lightening: a regnant myth or evidence-based verity?

Sidharth Sonthalia[1], Abhijeet K. Jha[2], Aimilios Lallas[3], Geraldine Jain[4], Deepak Jakhar[5]

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5 Consultant Dermatologist & Cosmetologist, New Delhi, India

Key words: glutathione, skin lightening, intravenous, GSH, GSSG

Citation: Sonthalia S, Jha AK, Lallas A, Jain G, Jakhar D. Glutathione for skin lightening: a regnant myth or evidence-based verity? Dermatol Pract Concept. 2018;8(1):15-21. DOI: https://doi.org/10.5826/dpc.0801a04

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Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

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JFDA

- Not allowed IV
- No allowed in micro-needling

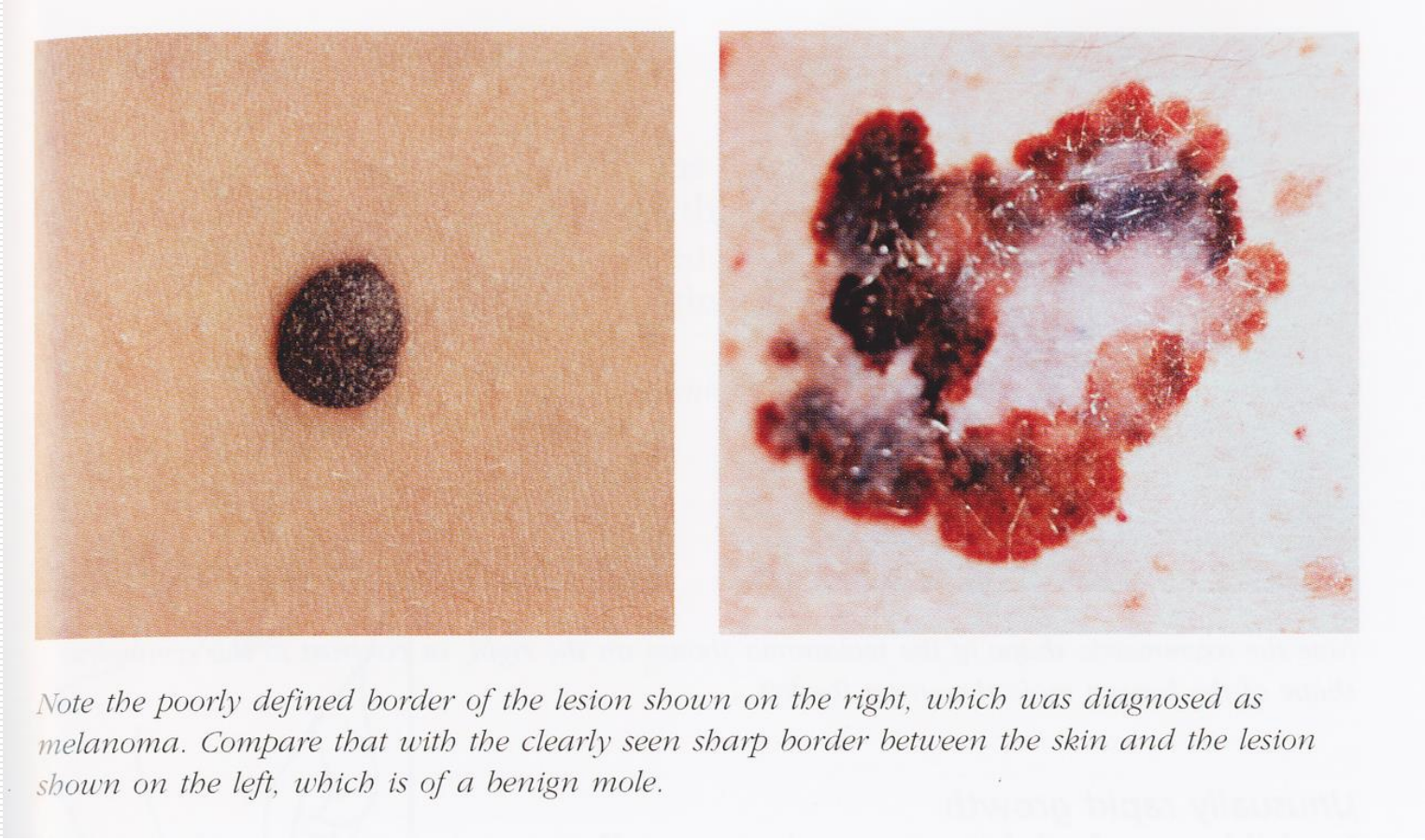
General remarks

- When using skin depigmenting agents:
- The sun should be avoided as much as possible
- Depigmenting preparations are meant to be applied only to the hyperpigmeted skin
- It could take months before any improvement can be seen
- More than one Depigmenting agent can be used for any given hyperpigmented lesion

General remarks

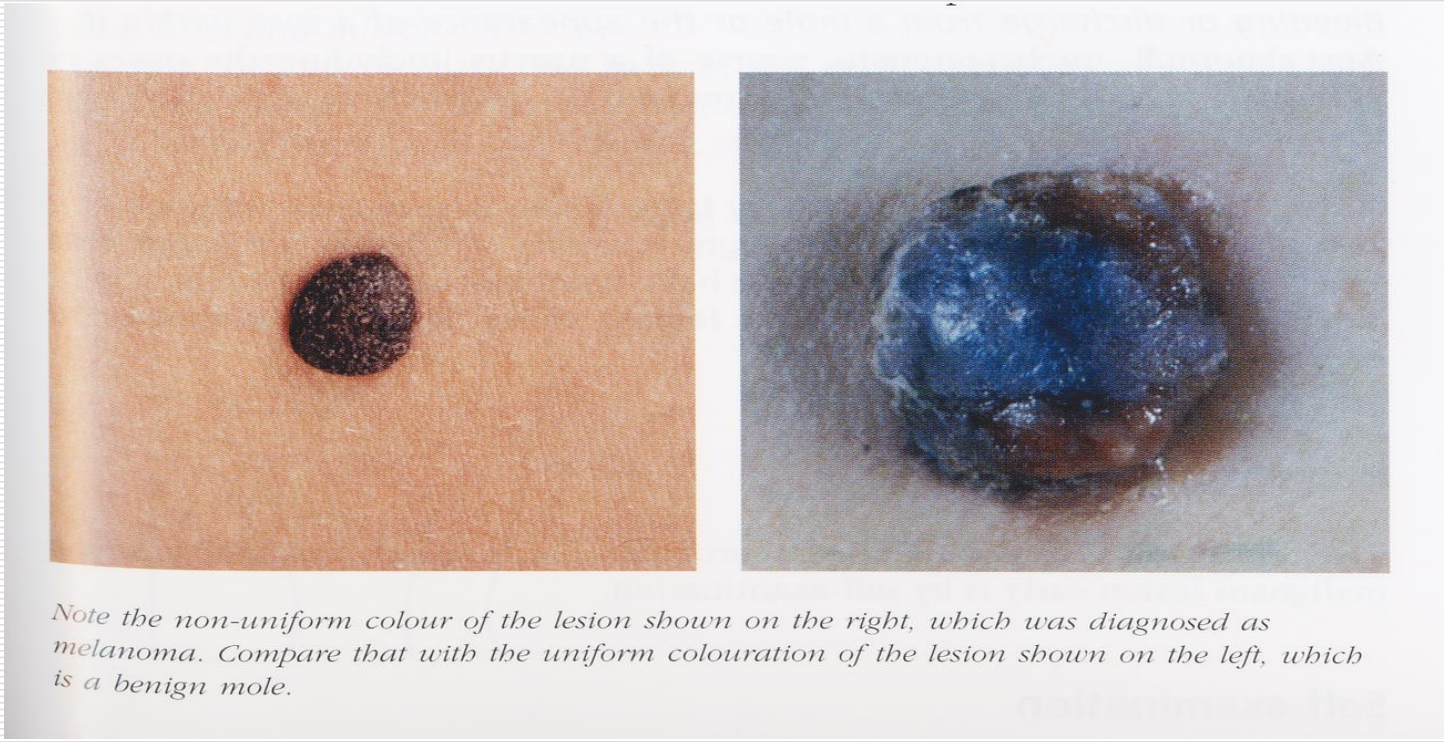
- Combination with retinoids, sunscreens, and chemical peels will enhance the effectiveness of these products
- Sometimes a hyperpigmented lesion is a malignant melanoma
- Malignant melanoma can develop from a melanocytic naevus (mole) or from skin that has been damaged by cumulative sun exposure or from healthy skin

A. Irregular, poorly defined edges



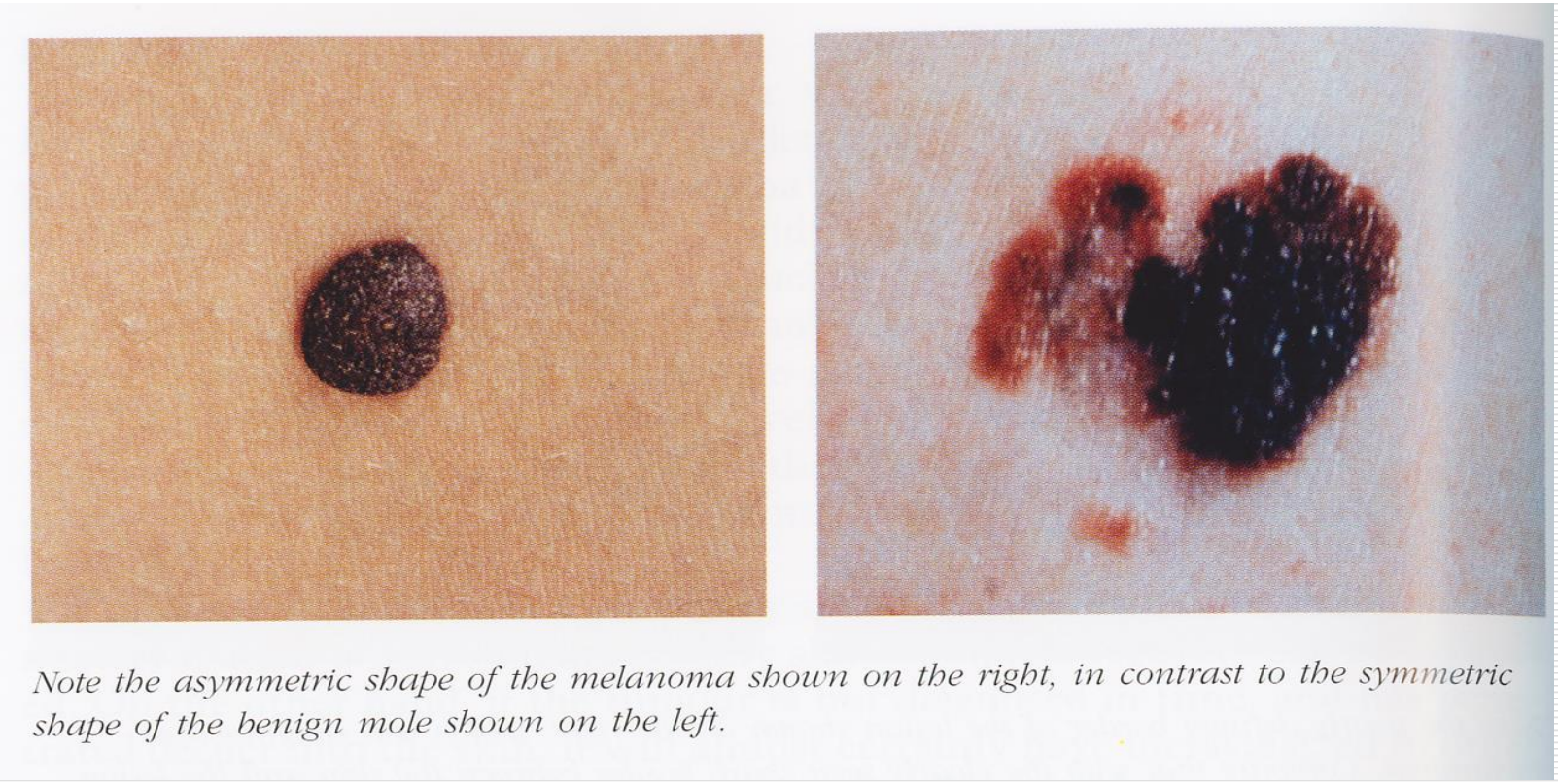
Note the poorly defined border of the lesion shown on the right, which was diagnosed as melanoma. Compare that with the clearly seen sharp border between the skin and the lesion shown on the left, which is of a benign mole.

B. Non-uniform coloration



Note the non-uniform colour of the lesion shown on the right, which was diagnosed as melanoma. Compare that with the uniform colouration of the lesion shown on the left, which is a benign mole.

C. Asymmetry of the lesion



Note the asymmetric shape of the melanoma shown on the right, in contrast to the symmetric shape of the benign mole shown on the left.

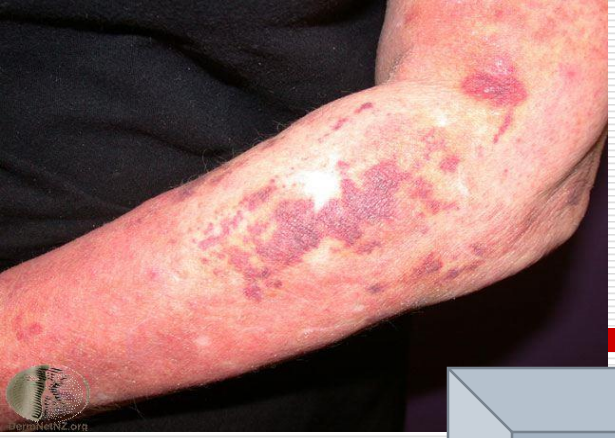
Malignant Melanoma

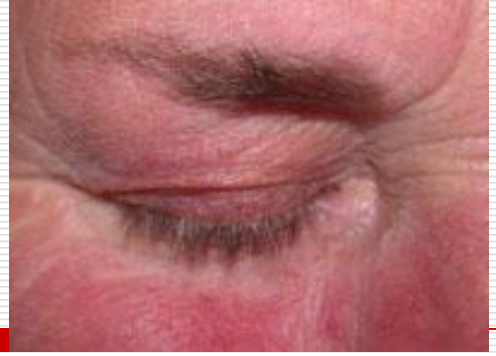
D. Unusually rapid growth

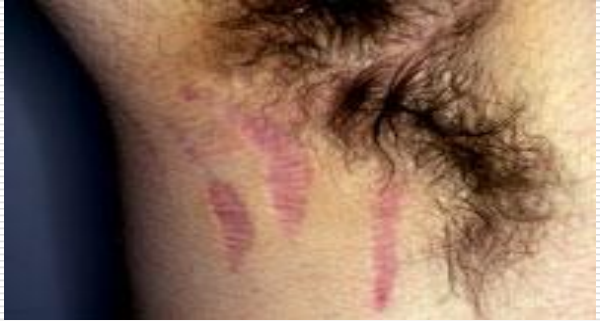
E. Bleeding or discharge from a mole or the appearance of a sore within it

Uncontrolled ingredients: Topical corticosteroids

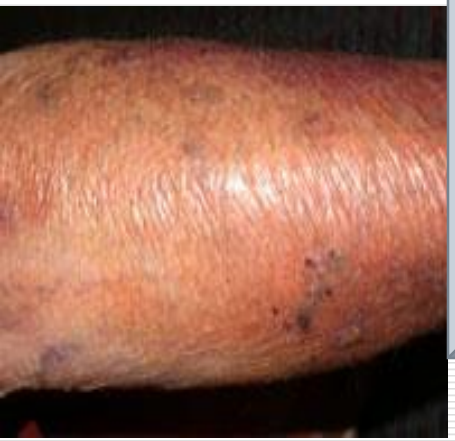
- Their prolonged use (> 3 weeks), especially on thin skin such as facial and flexural sites, is associated with a range of adverse effects.
- striae ,atrophy, peri-oral dermatitis, rosacea-like eruption, acne vulgaris, telangiectasia, cutaneous infection, poor wound healing, easy bruising and hypertrichosis

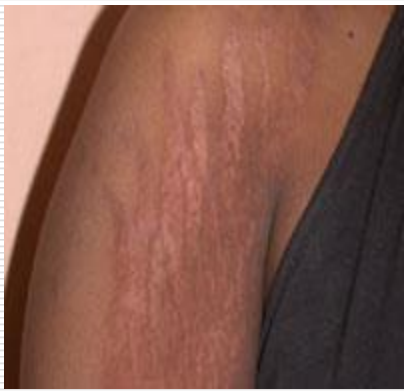


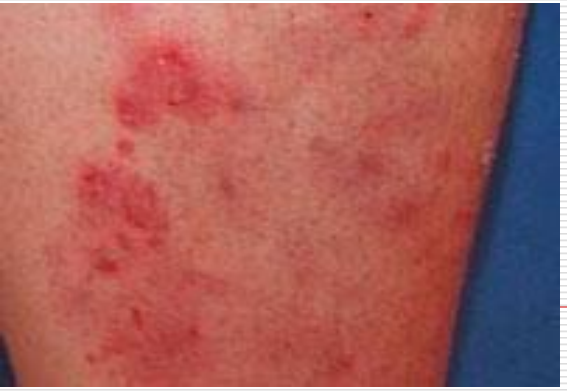


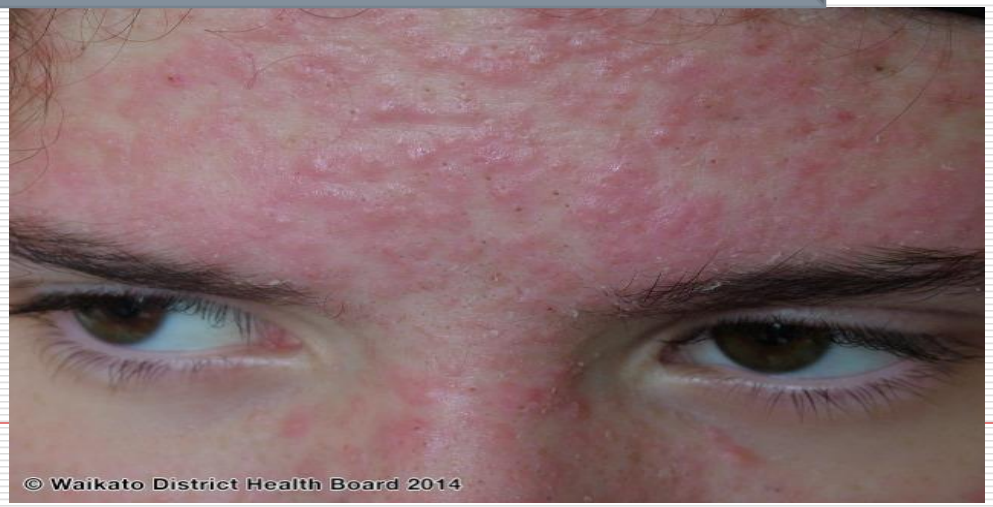


Pharmacists Role:
Topical steroids are just used as anti-inflammatory agents in a strict regulated protocol and not as lightening agents









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General remarks

- In the past, mercury was used for lightening skin lesions
- Mercury use is now prohibited because its highly toxic
- Some skin lightening products was found to contain mercury above the accepted level

Uncontrolled Ingredients: Mercury

http://www.fda.gov/forconsumers/consumerupdates/ucm294849.htm

For Consumers

Mercury Poisoning Linked to Skin Products

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En Español

On this page

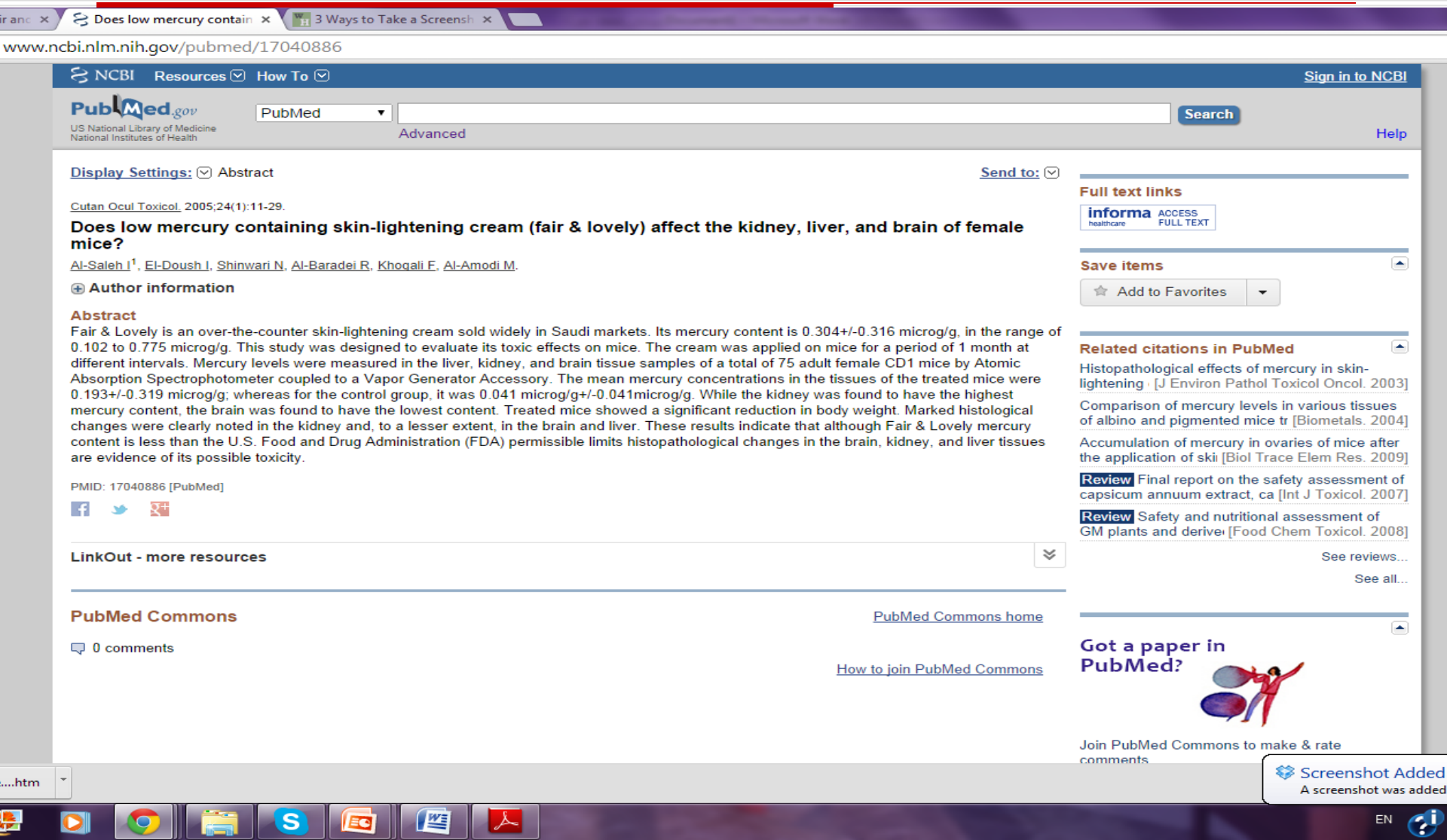
Federal health officials are warning consumers not to use skin creams, beauty and antiseptic soaps, or lotions that might contain mercury.

The products are marketed as skin lighteners and anti-aging treatments that remove age spots, freckles, blemishes and wrinkles, says Gary Coody, national health fraud coordinator in the Food and Drug Administration's Office of Regulatory Affairs. Adolescents also may use these products as acne treatments, adds Coody. Products with this toxic metal have been found in at least seven states.

The products are manufactured abroad and sold illegally in the United States—

Cutan Ocul Toxicol. 2005;24(1):11-29.

Does low mercury containing skin-lightening cream (fair & lovely) affect the kidney, liver, and brain of female mice?

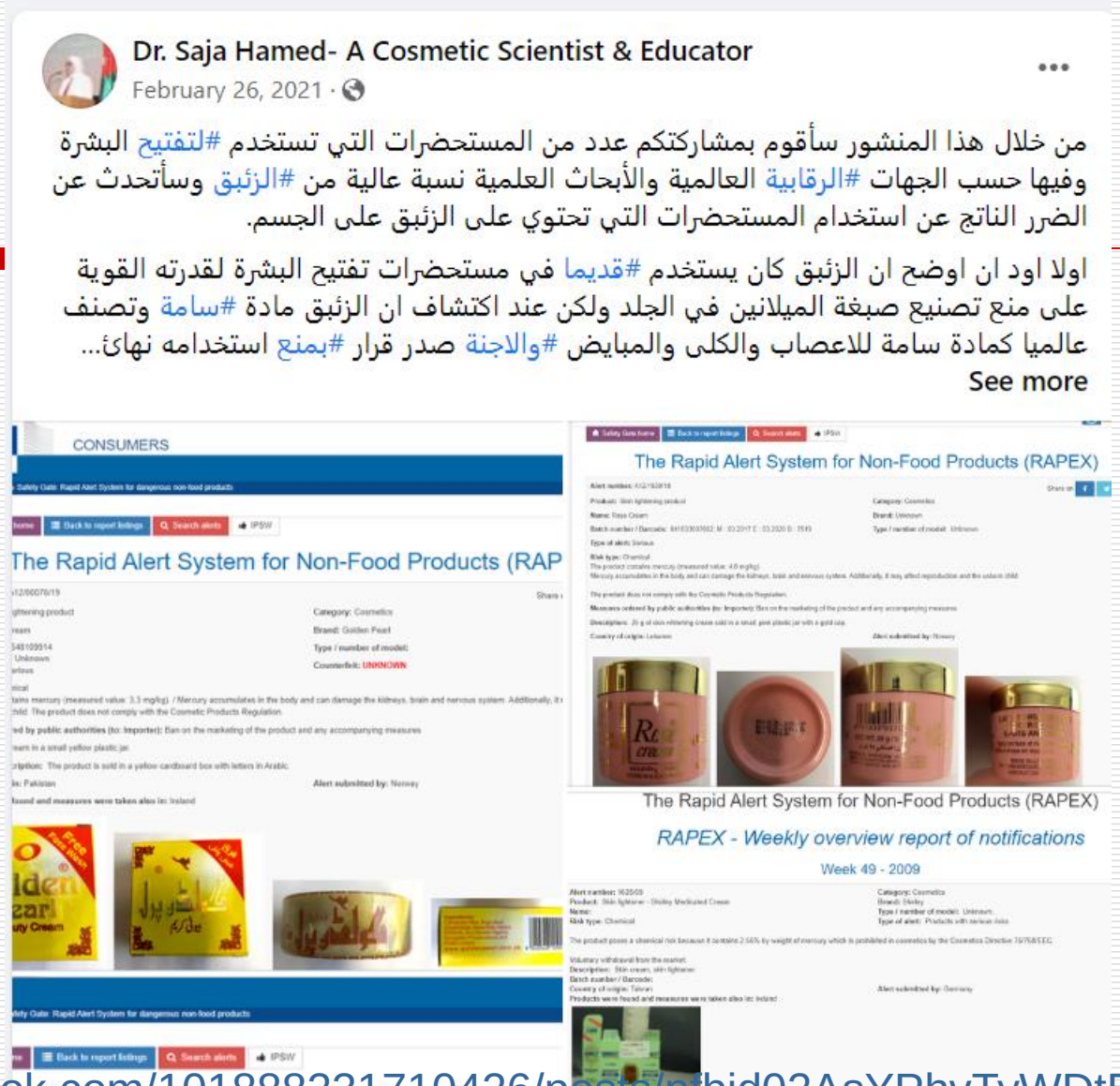


J Toxicol Environ Health. 1997 Jun 6;51(2):123-30.

Mercury content in skin-lightening creams and potential hazards to the health of Saudi Women.

Read

- Briefs about Mercury in Skin Lightening products PDF
- Products locally and internationally that contain Mercury



https://www.facebook.com/101888231710426/posts/pfbid02AsYPhvTyWDtRMrZrucTwRcBvVaQTY9Bqg2ffSYpfjbLRJZdVxu88XJvNMv7JK6QEl/?mibextid=cr9u03

- In July 2020, HUL renamed itskin care brand Fair & Lovely as Glow & Lovely after fairness products came under social pressure amid a global debate about racial inequality.

- 'Poisoning for profit' illegal skin whitening creams – BBC London – YouTube.

- Brief about Mercury in Skin Lightening products (See report)

https://www.cosmeticscare.eu/en/deoxyarbutin-ban-and-dihydroxyacetone-regulations/

Summer is in full swing, and the European Commission doesn't laze around and introduces further changes to the cosmetic law. Thus, the **Commission Regulation (EU) 2021/1099 of 5 July 2021** amending Annexes II and III to the Regulation (EC) No 1223/2009 was published. The changes concern two ingredients: Deoxyarbutin (INCI: Tetrahydropyranyloxy Phenol) and Dihydroxyacetone (INCI: Dihydroxyacetone). Details below.

Deoxyarbutin

Deoxyarbutin (**INCI: Tetrahydropyranyloxy Phenol**) has been used as a skin lightening agent so far, e.g. in face creams. It is a derivative of ß-arbutin, obtained by removal of hydroxyl groups from the glucose side-chain of ß-arbutin.

This compound has not been covered by the Regulation (EC) No 1223/2009 so far. However, the SCCS Scientific Committee concluded that, due to safety concerns, the use of deoxyarbutin in face creams up to 3% cannot be considered safe (opinion no. ***SCCS/1554/15***). This is due to the fact that deoxyarbutin releases **Hydroquinone**. On the other hand, Hydroquinone is a prohibited substance for use in cosmetics (Annex II of the Regulation 1223/2009, item 1339), with the exception of position 14 in the Annex III (it may be used only in artificial nail products under certain conditions).

All this made Tetrahydropyranyloxy Phenol (deoxyarbutin) included in the **Annex II**, under **entry 1657**. In brief, this substance will be banned for use in cosmetic products from **July 26th, 2021.**

Report

Skin-lightening practice among women living in Jordan: prevalence, determinants, and user's awareness

Saja H. Hamed[1], PhD, Reema Tayyem[1], PhD, Nisreen Nimer[1], MSc, and Hatim S. AlKhatib[2], PhD

[1]Faculty of Allied Health Sciences, the Hashemite University, Zarqa, Jordan, and [2]Faculty of Pharmacy, University of Jordan, Amman, Jordan

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Abstract

Background The use and misuse of skin-lightening products among women living in Arab communities have not been documented previously. This study investigates the determinants, the prevalence and users awareness associated with the use and misuse of skin-lightening products among women living in Jordan.

Method Female customers arriving at selected pharmacy stores were randomly asked to complete a questionnaire.

Results A total of 318 women completed the questionnaire, of which 60.7% reported the use of skin-lightening products. Users included women from different age and economic groups. Main reasons for use were preference of lighter skin tone, the treatment of hyperpigmentary disorders or both. More than a third of the users were not aware of the potential side effects of these products. A significantly larger proportion of skin-lightening product users believed that lighter skin tone plays a role in self-esteem, perception of beauty and youth, marriage and employment opportunities when compared with nonusers.

Conclusion Skin lightening is a common practice among women living in Jordan. It is reinforced by the association of lighter skin tone with a number of perceived benefits including perception of beauty, job and marriage opportunity. User's awareness regarding the safety of skin-lightening products and instructions for proper use are important considerations when developing interventions to control the misuse of these products.

Introduction

The use of skin-lightening products by women with dark skin tone is a common practice in the sub-Saharan Africa.[1–4] This practice has been reported to be associated with many side effects[5] including dermatological,[6] nephrological[7,8] as well as neurological complications.[9,10]

The occurrence of such adverse events in populations using these products is partially explained by the fact that a number of the available skin-lightening brands have been found to contain toxic substances such as mercury.[7]

Mercurials were popular as lightening agents until they were recognized as toxic. They have been shown to be nephrotoxic via the absorption of mercury through the skin following repeated use.[7,8] In addition, dermal exposure to skin-lightening creams containing mercury may contribute to infertility as a consequence to accumulation of mercury in the ovaries of treated mice.[11]

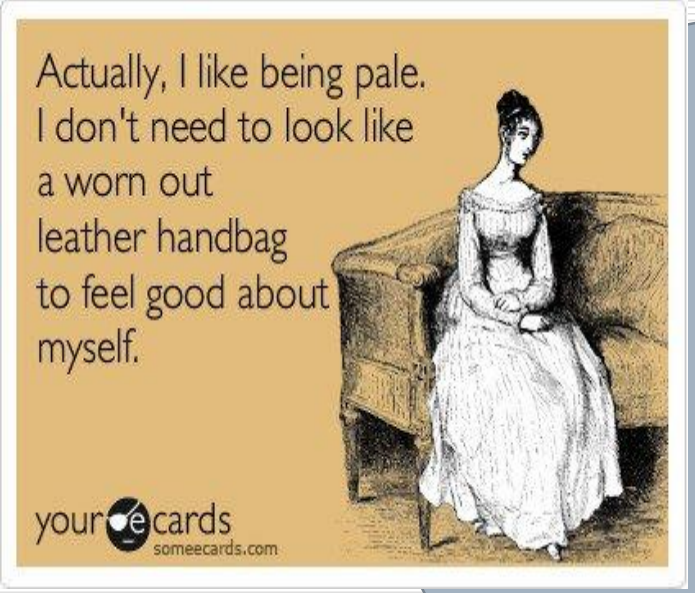
Although banned in many countries, a number of studies showed that a number of marketed lightening products still contain these compounds.[12,13] About 45% of commonly used skin-lightening creams in Saudi Arabia were shown to contain mercury above the FDA's acceptable limit of 1ppm.[14]

However, even with the best quality products containing approved components, mainly the ones containing hydroquinone, some of the dermatological side effects can be seen and they are usually associated with the misuse of these products.[15]

Hydroquinone, the depigmenting standard, has been banned in cosmetic use in Europe and currently available only by prescription. However, in other countries such as Jordan, hydroquinone use is still allowed in cosmetics at a concentration level not more than 2%. Cases of exogenous ochronosis caused by the abuse of hydroquinone-containing products have been reported.[16] It is characterized by progressive darkening of the area to which the cream containing hydroquinone is applied. Such cutaneous side effect is of great importance as it is difficult to treat and is disfiguring.[17,18]

Health problems secondary to skin-lightening practice, unrecognized, add a load on health care authorities and services in countries where this practice is common.

Prof Saja Hamed



We need to teach our children:
Our varied shades are expressions of our creator
Dark is Beautiful: Learning to Love the Skin I'm In
Shed our bias and value humanity
Stop Media and Ads that show this bias and engrave it into our little ones

Ads in India lauding fair skin 'degrading'

Watchdog issues guidelines to prevent discrimination against darker-skinned people

Published on
Aug 31, 2014

An ad for the Fair & Lovely cream more successful in love and caree generates more than S$500 million in revenue a year. -- PHOTO: FAIR & LOVELY

An ad for the Fair & Lovely cream. The perception in India th industry in fairness products that generates more than S$500 milli

By Nirmala Ganapathy, India Correspondent In New Delhi

It is a multimillion-dollar industry that panders to those obsessed with achieving a lighter skin tone, but India's advertising standards authorities have now stepped in to make sure its ads are, well, fair.

Take this commercial: A young woman in a dance show is relegated to a corner, all


Dark Is Beautiful
Saja
Home 6
DOES A FAIRNESS PRODUCT MAKE YOU FEEL
Say NO to skin colour bias!
tell us how you feel by writing to
disbcampaign@womenofworth.in
UNATTRACTIVE UNSUCCESSFUL OR UNLOVELY?
DARK is beautiful
/disbcampaign
www.womenofworth.in
Dark Is Beautiful
Community
Like
Follow
Message
Timeline
About
Photos
Email Signup
More
PEOPLE
39,154 likes
Invite your friends to like this Page
Post
Photo / Video
Write something on this Page...
Dark Is Beautiful shared a link.

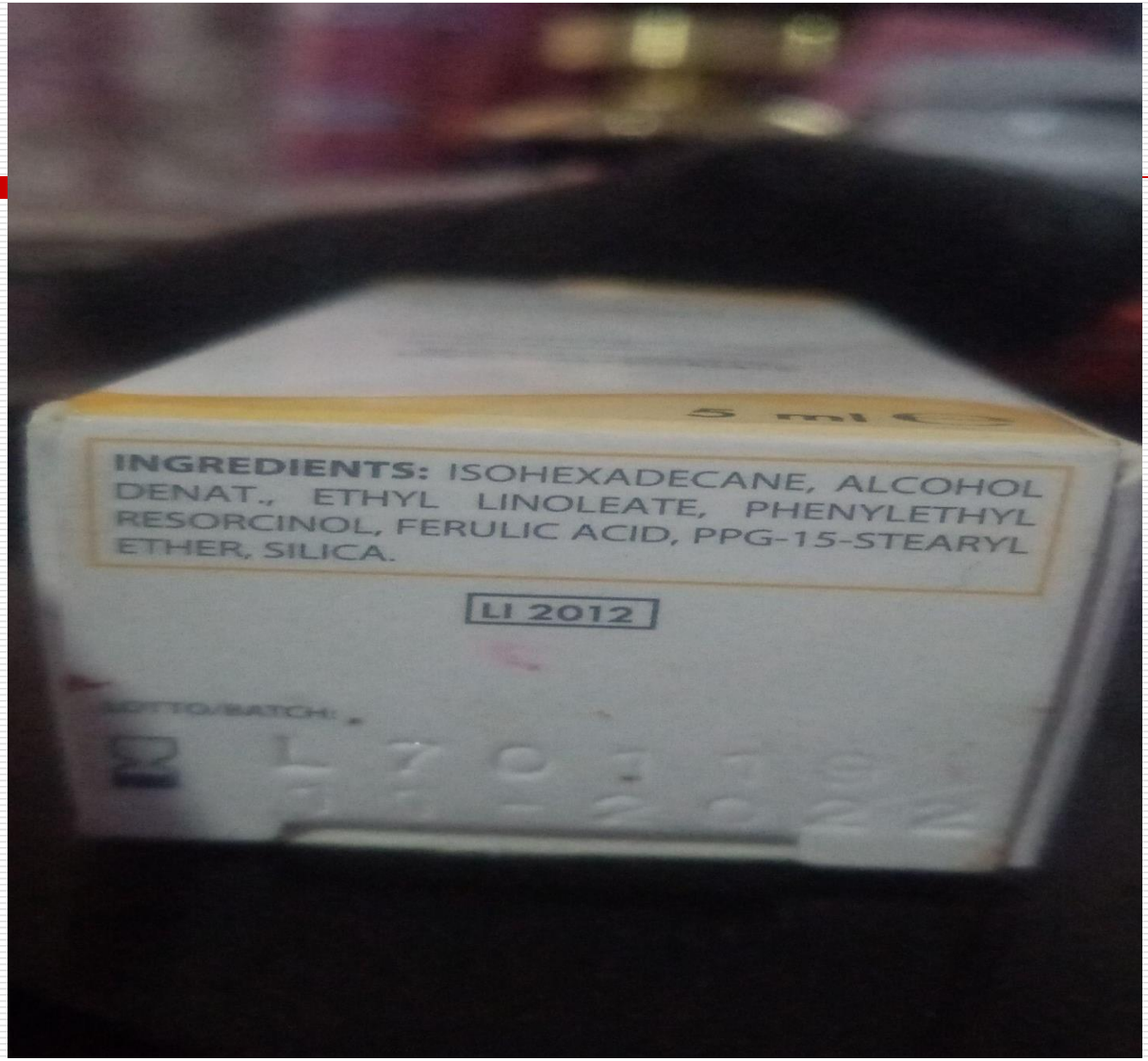
Aqua, Glycerin, Caprylic/Capric Triglyceride, Niacinamide, Sodium Acrylates Copolymer, Lecithin, Aluminum Oxide, Hydrogenated Polyisobutene, Phospholipids, Polyglyceryl-10 Stearate, Helianthus Annuus (Sunflower) Seed Oil, Shea Butter, Tartaric Acid, Disodium EDTA, Sodium Sulfite, Sodium Metabisulfite, Butylene Glycol, Saxifraga Sarmentosa Extract, Carica Papaya (Papaya) Fruit Extract, Psidium Guajava Fruit Extract, Phenoxyethanol, Capryloyl Glycine, Undecylenoyl Glycine, Microcitrus Australasica Fruit Extract, Xanthan Gum, Pentaerythrityl Tetra-Di-T-Butyl Hydroxyhydrocinnamate, Citric Acid, Nonapeptide-1, Perfume

Distilled Water, Cetyl Stearyl Alcohol, Glyceryl Monostearate, Glutathione, Kojic Acid, Fragrance Essential Oil, Phenoxyethanol

INGREDIENTS

2021547 8 - INGREDIENTS: AQUA/WATER/EAU, PROPANEDIOL, DIMETHICONE, CETEARYL ETHYLHEXANOATE, NIACINAMIDE, AMMONIUM POLYACRYLOYLDIMETHYL TAURATE, DIPOTASSIUM GLYCYRRHIZATE, HYDROGENATED LECITHIN, POTASSIUM PHOSPHATE, CERAMIDE NP, CERAMIDE AP, CERAMIDE EOP, CARBOMER, CETEARYL ALCOHOL, BEHENTRIMONIUM METHOSULFATE, DIMETHICONOL, LECITHIN, SODIUM CITRATE, RETINOL, SODIUM HYALURONATE, SODIUM LAUROYL LACTYLATE, CHOLESTEROL, PHENOXYETHANOL, ALCOHOL, ISOPROPYL MYRISTATE, CAPRYLYL GLYCOL, CITRIC ACID, TRISODIUM ETHYLENEDIAMINE DISUCCINATE, PENTYLENE GLYCOL, PHYTOSPHINGOSINE, XANTHAN GUM, POLYSORBATE 20, ETHYLHEXYLGLYCERIN (CODE F.I.L. D233672/1)

Active Ingredients: Hydroquinone (2%)
Inactive Ingredients: Water, Mineral Oil, Glyceryl Stearate, Cetyl Alcohol, Isopropyl Myristate, PEG-100 Stearate, Propylene Glycol, Cetearyl Alcohol, Polysorbate 60, Sodium Metabisulfite, Stearic Acid, Tocopheryl Acetate, Beta-Carotene, Diazolidinyl Urea, Iodopropynyl Butylcarbamate, Fragrance


5 ml
INGREDIENTS: ISOHEXADECANE, ALCOHOL DENAT., ETHYL LINOLEATE, PHENYLETHYL RESORCINOL, FERULIC ACID, PPG-15-STEARYL ETHER, SILICA.
LI 2012

Prof Saja Hamed

Ingredients: Water (Aqua), Kaolin, Juglans Regia (Walnut) Shell Extract, Aloe Barbadensis (Aloe Vera) Leaf Extract, Stearic Acid, Glycerin, Isopropyl Myristate, Bentonite, Cetearyl Alcohol, Fragrance, Xanthan Gum, Methylparaben, Curcuma Longa (Turmeric) Rhizome Extract, Imidazolidinyl Urea, Sodium Lauryl Sulphate, Propylparaben, Hedychium Spicatum (Spiked Ginger Lily) Rhizome Extract, Alpinia Galanga (Greater Galangal) Rhizome Extract, Disodium EDTA, Crocus Sativus (Saffron) Flower Extract.

Micro-needlings

- Minimal invasive procedures
- Tiny needles puncture top layer of skin
- Tiny micro-wound
- New bed for healing and rejuvenation of skin
- Needs well controlled study for efficacy and safety
- Never do it at home by yourself (Dermarollers)
- and never apply topical products while using it
- (create wound and open up for complications like infection, scar worsen discoloration)….
- Microneedling Devices | FDA
- Mesotherapy: Procedure, Side Effects, and More (healthline.com)

Factors that participate in the color under eyes

- The quality of the skin: thin skin in this area allows the blood vessels to become more visible

- depending on the natural anatomy of your face as governed by your genetic the visibility of theses vessels may be more noticeable

Factors that participate in the color under eyes

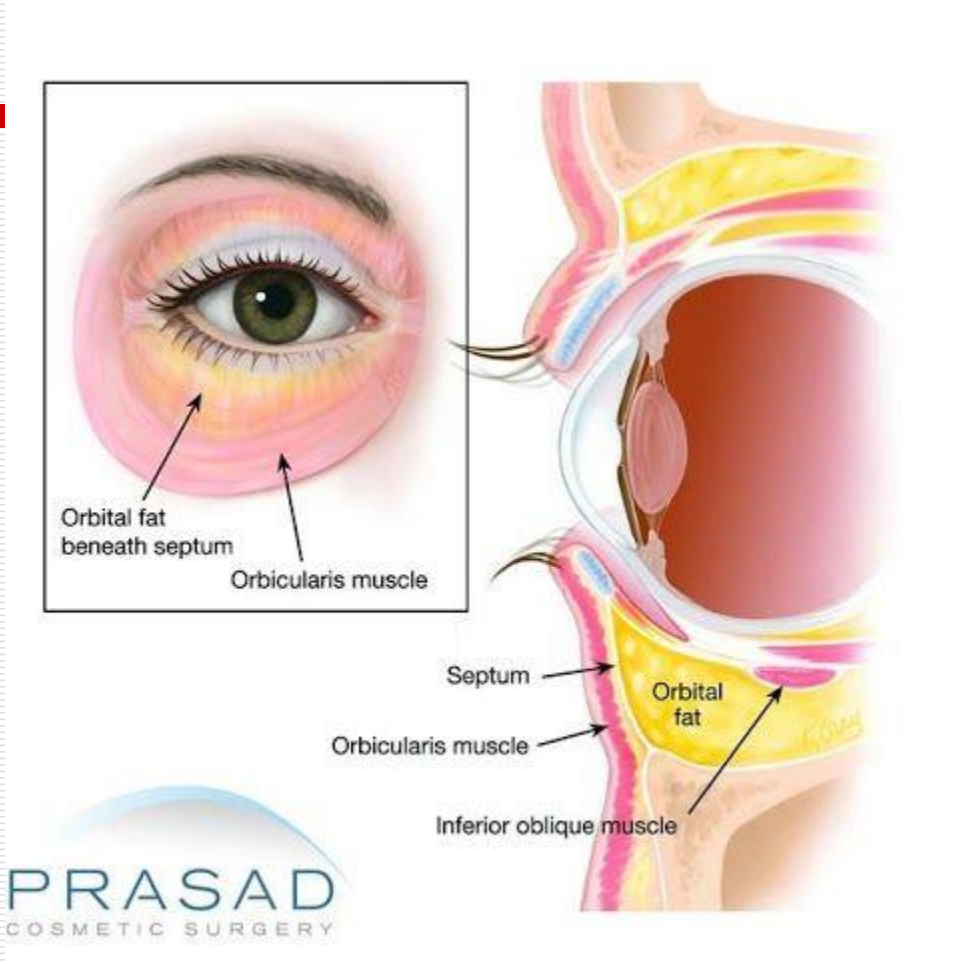
- Vey easy for the fluid to accumulate in the small confined compartment around the eye particularly from chronic rubbing of the eyes, irritation from cosmetics and eye creams
- The natural contour around the eyes and orbital brims as well as hollows that is influenced by underlying facial ligaments, bony structure and subcutaneous fatty tissue

Factors that participate in the colour under eyes

- natural contour around the eyes and orbital brims as well as hollows lend themselves to shadowing when light is reflected from these contours and concavity
- Overhead lightening can really worsen the noticeability of theses shadows whereas direct lightening can mitigate them substantially
- Also the skin around the eye can become hyperpigmenated by many factors such as melasma and congenital deeper pigment deposition, too much sun, hormonal changes, OC pills, topical compounds to grow lashes as LATISSE®

Factors that participate in the colour under eyes

- Age changes in structure, collagen and bone structure contribute to noticeability of under eye circles
- SO there are many factors that contribute to under eye color (anatomy, skin, chronic irritation from too many cosmetics or eye creams, age related changes, hormonal changes, fluid accumulation…etc)


Orbital fat
beneath septum
Orbicularis muscle
Septum
Orbital
fat
Orbicularis muscle
Inferior oblique muscle
PRASAD
COSMETIC SURGERY

Remarks: Under-Eye Circles:

- A common complaint by both men and women
- People with skin type IV and above inherit a genetic tendency to deep pigmentation around the eyes
- Any inflammation or vasodilation in this area may manifest as darkening
- Age changes

- Hence there are no global creams that can eradicate dark discoloration under the eyes
- Seek Medical consultation

Products:

- Elson & NacHT (1999) evaluated the use of vitamin K combined with retinol 0.15% for the treatment of periorbital hyperpigmentation and demonstrated that this preparation was effective in improving under-eye circle *(Elson M. and NacHT S: Treatment of periorbital hyperpigmentation with topical **vitamin K/vitamin A.** Cosmetic Dermatology, 12 (12): 32, 1999)*

Products

- Vitamin K (Phytonadione) is a fat soluble vitamin play a role in blood clotting's has anti-inflammatory properties
- Topical vitamin k has been shown to improve wound healings since it has antioxidant properties and help in wound contracture
- Some evidence (not 100%) because these studies are small and use products that have others ingredients (not just vitamin K)

Products

- The directive 2009/06/EC of 4 February 2009 prohibits the use of phytonadione in all cosmetic products put on the market of the European Union.

- The prohibition of phytonadione (a man-made form of vitamin K) in cosmetic products is due to the fact that this substance may cause cutaneous allergy

Products

- If your dark circles are hereditary vit k will not do any things

Products

- Make up and concealers
- Make up that add green pigments can counter balance and redness and mask it
- Optical diffusers to make up and concealers that function to reflect light away and conceal contour irregularities (boron, mica, nylon, polymethylmethacrylate, polyurethane, silica, silicone powder, talc, Teflon, titanium dioxide, zinc oxide)
- However, using cosmetics and concealers can increase risk of irritation as well as some individual become sensitized to one of these ingredients and develop allergic contact dermatitis so it will increase inflammation and swelling and discoloration and exacerbate underlying discoloration

Products

- The most effective and useful eyecream is a sunscreen since discoloration is driven and worsen by chronic sunexposure
- Sunscreens can be irritating and many may endorse burning/ stinging of the eyes and excessive irritation when trying to put sunscreens around the yes → thus look for mineral sunscreens→ scatter light and mitigate the appearance of dark discoloration

Products

- Topical creams for dark spot and melasma: retinoids (vitamin A derivatives), arbutin, kojic acid, soy, niacinamide→ may potentially be helpful but also may contribute to worsening irritation also these ingredients are not well studied for discoloration under the yes so inadequate objective data to say 100% that products containing these ingredients are worth the investment

Products

- Caffiene: can transiently constrict the blood vessels this improve eyelid swelling and resulted fluid accumulation and transiently decreased noticeable blood vessels around the eyes (**transient not cure**) and again added risk of irritation and worsening the dark circle

Medical interventions

- A variety of Laser based and light based therapy include intense pulse light, radiofrequency, pulse dye laser or vascular laser that target blood vessel around the eye, and laser that target discoloration
- Medical tattooing by trained physcians (place pigment in the deeper layer of the skin that can improve the color
- Fillers (by trained physician): impt appropriate filler selection and appropriate placement of the filler (have risks) also fat transfer.

- No one size fits all approach
- Impossible to recommend eye cream
- Most eye creams are overpriced moisturizers
- Cosmetic companies claim that their creams erase dark circles
- These creams may contain depigmenting agents; however, it is unproven whether this condition is caused by excessive melanin production
- Sunscreen and increased rest
- There are currently no available and effective treatments
- Lasers can cause some improvement

- Water, dimethicone, glycerin, cetearyl olivate, polyacrylamide, sorbitan olivate, phenoxyethanol, dimethicone/vinyl dimethicone crosspolymer, synthetic beeswax, C13-14 isoparafin, dimethiconol, carbomer, dimethicone crosspolymer, chlorphenesin, laureth-7, sodium hyaluronate, ethylhexylglycerin, C12-14 pareth-12, sodium hydroxide

Neutrogena Hydro Boost Hydrating Gel Eye Cream with Hyaluronic Acid, Dermatologist Recommended Water Gel Under-Eye Cream

Hydraluron Moisture Boosting Facial Serum 30ml

- Water, Propanediol, Sodium Hyaluronate, Carbomer, Phenoxyethanol, Butylene Glycol, Sodium Hydroxide, Ahnfeltia Concinna Extract, Disodium Edta, Phenoxyethanol

Dark Circle Relief Cream 1 Percent Vitamin K Oxide

- Water, Ethyl Alcohol, C12-15 Alkyl, Benzonate, Caprylic/Capric Triglyceride, Parafinum Liquidum, Cyclomethicone, Glycerin, Lecithin, Sodium PCA, MICA, Phospholipids, Phytonadione Epoxide Hexane, Titanium Dioxide, Polysorbate 20, Acrylates/Acrylamide Copolymer, Phenoxyethanol, Acrylates/C10-30 Alkyl Crosspolymer, Triethanolamine, Carbomer, Disodium EDTA, Propylparaben, Methylparaben, BHT, BHA.

Purified water, Green tea extract*, Aloe barbadensis (Aloe vera) gel*, Centella asiatica (Gotu kola)* extract, Gingko biloba leaf extract, Caprylic/capric triglycerides, Prunus amygdalus dulcis (Sweet almond) oil*, Persea gratissima (Avocado) oil*, Sesamum indicum (Sesame) seed oil*, Glyceryl stearate, Vegetable glycerin, Hyaluronic acid, Sodium PCA, Dimethicone Copolyol, Wheat protein amino acid (and) Silk protein hydrolysate, Extracts of Chamomile*, Ginseng*, Eyebright, Evening primrose (and) Borage oil, Retinyl palmitate (Vitamin A), Beta glucan, Phytomenadione (Vitamin K), and Vitis vinifera (Grape) seed extract*.

Hyaluronic acid serum..Remarks