

In The Name Of GOD



Melasma

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Introduction

- ▶ Common acquired
- ▶ symmetrical hypermelanosis
- ▶ Complex pathogenesis (beyond melanocyte)
- ▶ Now consider as photo aging feature

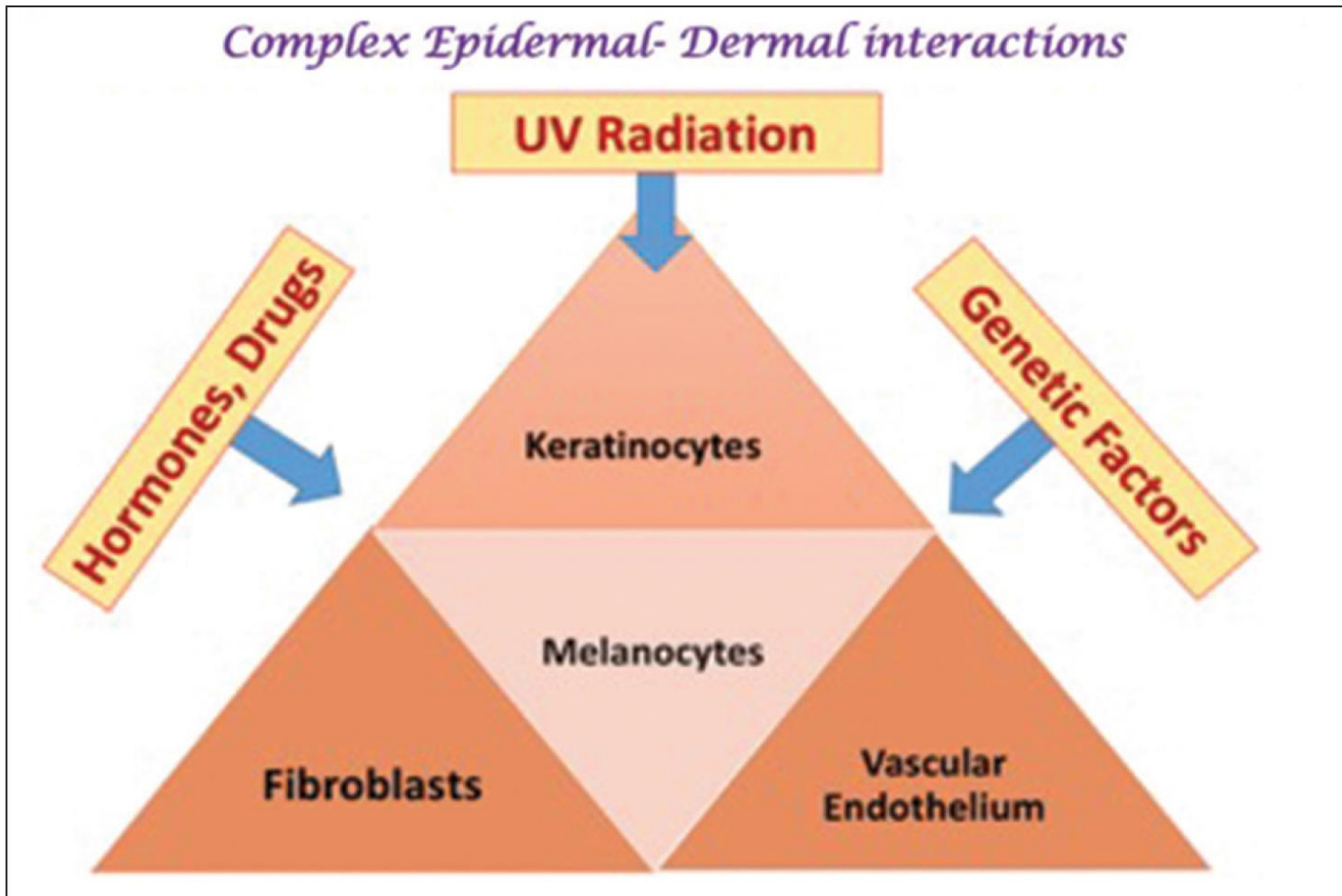


Figure 1 : Melasma – pathogenesis: A complex interaction among epidermal and dermal entities

Epidemiology

- ▶ Most common in women
- ▶ Skin types III-V
- ▶ Areas with increased UV light
- ▶ thirties and forties
- ▶ Rarely seen in men

Clinical Sign

- ▶ light-to-dark brown on sun-exposed area
- ▶ Irregular macules or patch bilaterally
- ▶ face usually forehead and malar areas
- ▶ Less frequently forearm
- ▶ earlier classified (Melanosome localization)
 - ▶ epidermal
 - ▶ dermal
 - ▶ Mixed

Now: all are mixed

Pathogenesis & Pathology

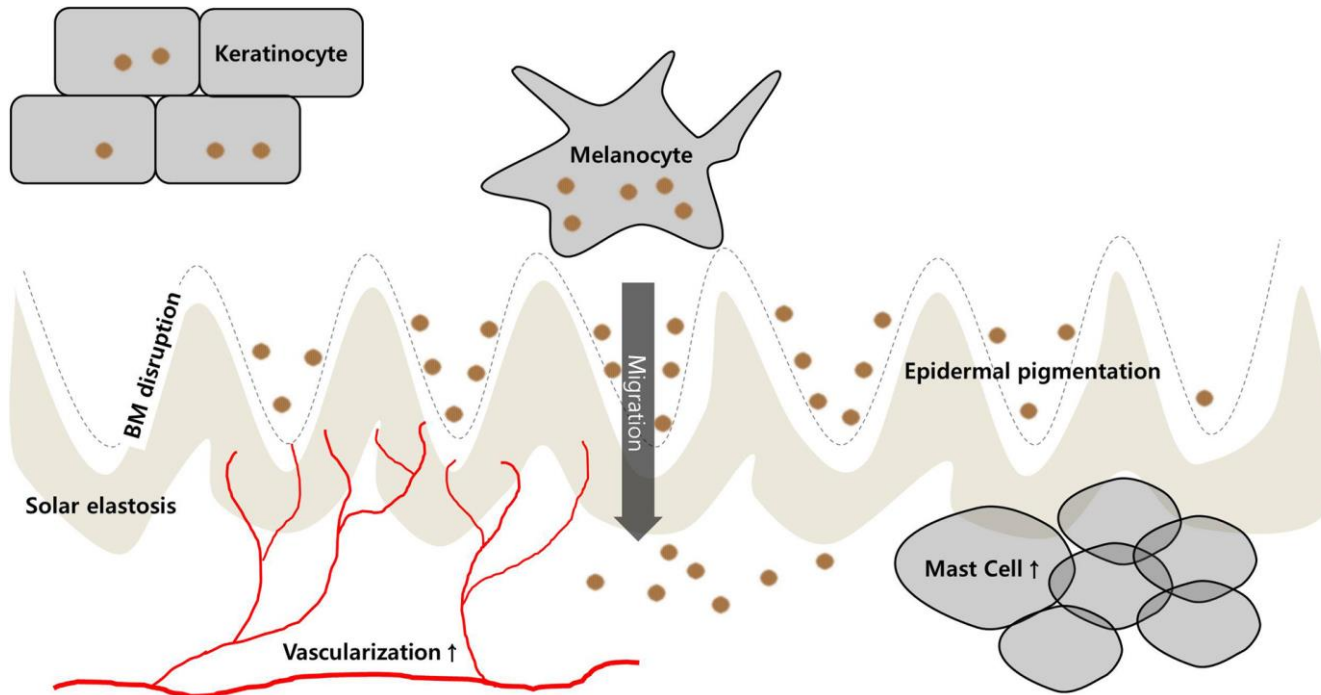


Figure 1-Schematic view of histological changes in melasma. The amount of melanin is significantly increased in all epidermal layers. Basement membrane is disrupted and thinned, facilitating migration of melanocytes and melanin into the dermis. Melanocytes protruding into the dermis along with a disrupted basement membrane are a characteristic feature of melasma. Solar elastosis is prominent, and the number of mast cells is significantly increased in the dermis. The number of blood vessels, vessel size and vessel density are greater in lesional melasma skin than in perilesional skin

Pathogenesis & Pathology

TABLE 1 A comparison of histological findings in melasma and SL

	Melasma	SL
Melanin	↑ in epidermis/dermis	↑ in epidermal basal layer
Number of melanocytes	↑ or no change	↑ (due to epidermal hyperplasia)
Rete ridge elongation or epidermal thickening	(-)	(+)
Solar elastosis	(+)	(+)
Dermal melanophage	(+)	Scant, but observed abundantly in some cases
BM disruption	(+)	(-)
Vascularization	↑	↑(reported in one study)
Mast cell	↑	(-)

Pathogenesis & Pathology

Melanocyte

- ▶ Increase amount of melanin production (Melanogenesis)
 - ❖ Not increase in number of melanocyte
- ▶ Hyper active melanocyte in lesion of melasma
 - ❖ increased dendrites, mitochondria, golgi bodies, and rough endoplasmic reticulum (RER)
 - ❖ So they are biologically active
 - ❖ Produce more melanin & induce melanogenesis
- ▶ Up regulation of MSH receptor (MC1-R) due to UV
 - ❖ Proopiomelanocortin (POMC) cleaved to produce & MSH & ACTH due to UV
 - ❖ These binds to MC1-R and increase PKA
 - ❖ Increase cAMP and then activate MITF

Pathogenesis & Pathology

Melanocyte...

- ▶ MITF controls expression of tyrosinase
 - ❖ Tyrosinase through several steps Transform DOPA to eumelanin and pheomelanin
- ▶ UV generate 1,2-diacylglycerols (DAGs), a second messenger in membrane of melanocyte to phospholipase C and D
- ▶ Activate tyrosine
- ▶ Tumor suppressor protein p53 upregulates POMC in keratinocyte post UV damage

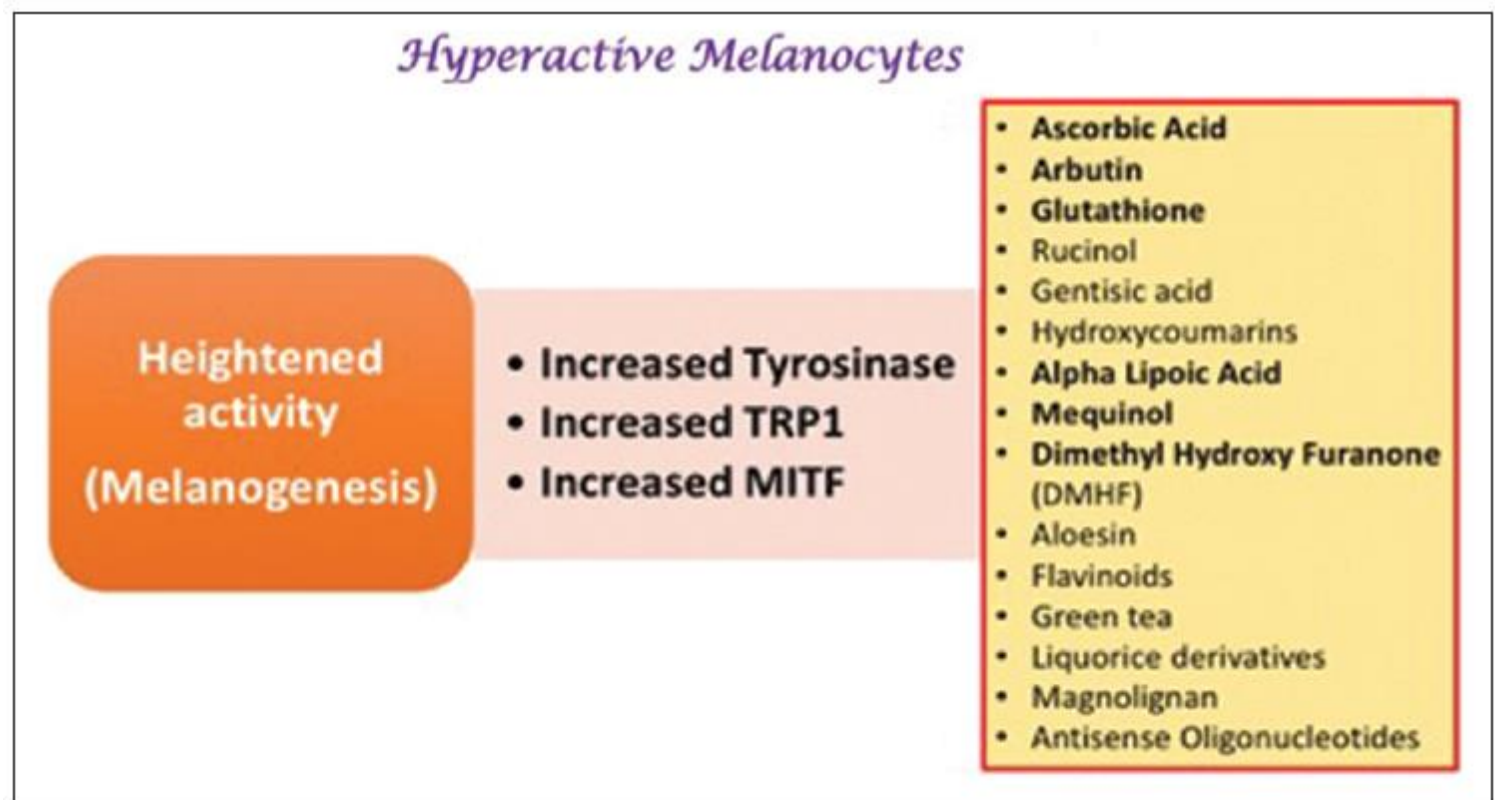


Figure 2: Pathway of melanogenesis and the role of the DHI:DHICA ratio

Pathogenesis & Pathology

Inflammation

- ▶ Dermal inflammation Activate fibroblasts
 - ❖ Secrete stem cell factor
 - ❖ C-kit (stem cell factor receptor) upregulated
 - ❖ C-kit & SCF activate tyrosine kinase
- ▶ Inflammation increase COX-2 and prostaglandins and stimulate melanocyte

Role of Oxidative stress

**UV + IR+
Visible
light**

- **Reactive O₂ species**
 - Increased MMP 1 , 9
 - Solar elastosis
 - Basement membrane damage

- **Vitamin A**
- **Vitamin E**
- **Vitamin C**
- **Niacin**
- **Glutathione**
- **N-nicotinoyl dopamine**
- **Oral proanthocyanidine**
- **Pycnogenol**
- **Polyphenols**
- **Epigallocatechin-3-gallate**

Figure 3: Role of drugs with antioxidant and anti-inflammatory activity

Pathogenesis & Pathology

Melanosome transfer

- ▶ Transfer of melanosome from epidermal melanocyte to neighboring keratinocyte
- ▶ protease-activated receptor 2 (PAR-2) in keratinocyte have an important role

Melanosomal transfer to Keratinocytes

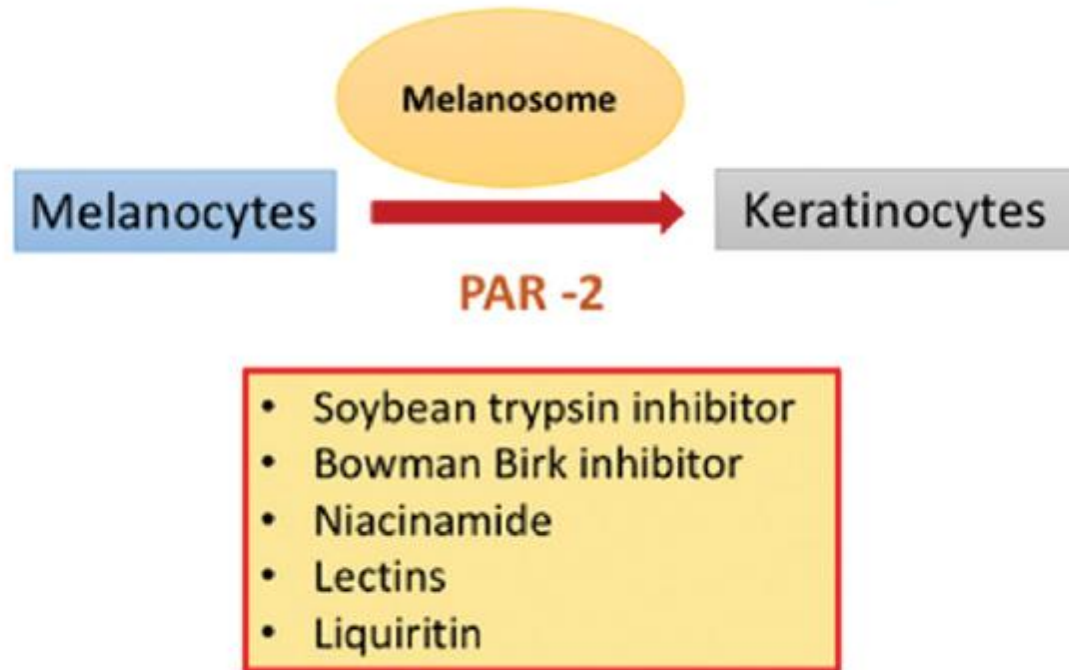


Figure 4: Role of a defective skin barrier in melisma

Pathogenesis & Pathology

Defect of Skin Barrier

- ▶ Due to UV or *de novo*
- ▶ Impaired stratum corneum integrity
- ▶ downregulation of some genes in lipid metabolism
 - ❖ peroxisome proliferator-activated receptor alpha
- ▶ impaired production of free fatty acids leading to disrupted barrier

Role Of A Defective Barrier Function

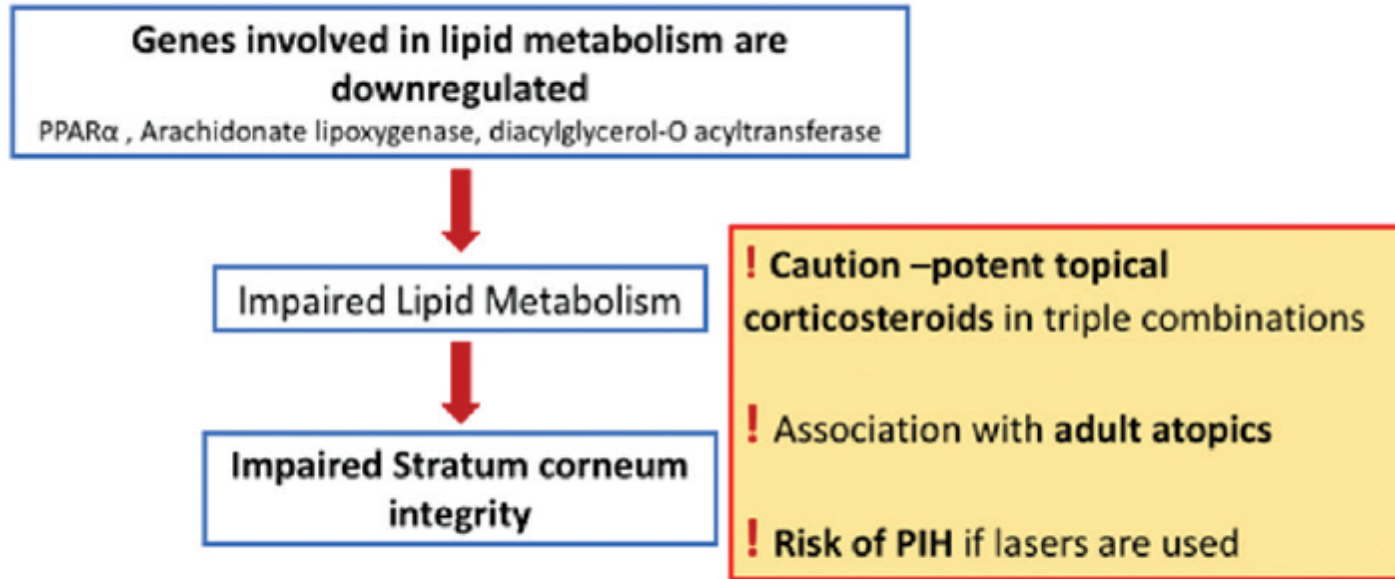


Figure 5: Role of vascular endothelium and mast cells – tranexamic acid inhibits the plasminogen pathway and decreases the activity of mast cells. Zinc primarily affects mast cell degranulation

Pathogenesis & Pathology

Vascular Component

- ▶ Increased VEGF synthesis result in proliferation of dermal vessels.
- ▶ VEGF receptor on melanocytes.
- ▶ melanin synthesis increase
- ▶ UV induce release plasminogen from dermal vessels and induce melanogenesis

Pathogenesis & Pathology

Mast Cell

- ▶ Higher in Melasma
- ▶ UV increase histamine release
 - ❖ Bind to H2 receptor that activate tyrosinase pathway
- ▶ UV induces production of mast cell tryptase
 - ❖ Activate MMP precursors
 - ❖ Damage the BM
 - ❖ Tryptase contribute solar elastosis
- ▶ Granzyme B from mast cells damage ECM further
- ▶ mast cells induce hypervascularization, by secreting angiogenic factors: vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and transforming growth factor-B (TGF-B).

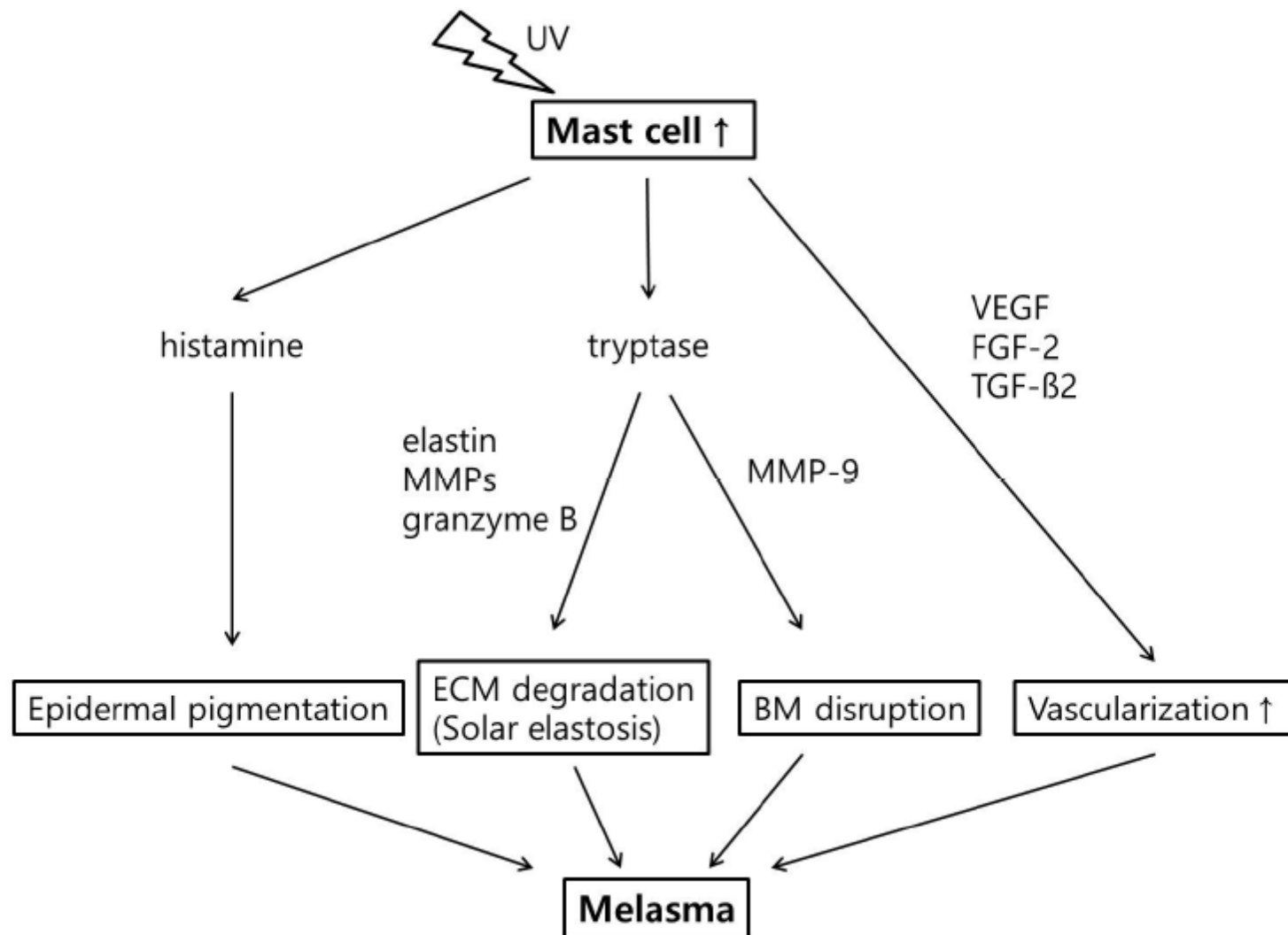


Figure 1. The role of mast cells in melanogenesis and photoaging. UV= ultraviolet; MMPs = matrix metalloproteases; VEGF = vascular endothelial growth factor; FGF-2 = fibroblast growth factor-2; TGF- β = transforming growth factor- β ; ECM = extracellular matrix; BM = basement membrane.

Pathogenesis & Pathology

Basement Membrane Damage

- ▶ key role in melasma
- ▶ UV damage activates MMP2
 - ❖ Degrade type IV and VI collagen in the basement membrane
- ▶ Cadherin 11 upregulated in melasma
 - ❖ Mediate interaction of fibroblast and melanocyte
 - ❖ Increase melanogenesis
- ▶ allow moving of melanocyte and melanin granules to dermis
- ▶ Make melasma persist
- ▶ trauma induced lasers or other therapies that further damage basement membrane may worsen the disease

Pathogenesis & Pathology

Solar Elastosis

- ▶ accumulation of abnormal elastic tissue in dermis
- ▶ chronic sun exposure
 - ❖ high level of solar elastosis in melanosome
- ▶ UVB exposure can stimulate keratinocytes to secrete several growth factor
- ▶ these GF can increase melanin production
- ▶ GF like inducible nitric oxide synthase and plasmin
- ▶ They lead to higher level of arachidonic acid and α -MSH and melanin

Pathogenesis & Pathology

Hormones

- ▶ Estrogen play a role in melasma
- ▶ increased number of estrogen receptor in dermis in melasma
- ▶ increased number of progesterone receptor in epidermis in melasma
- ▶ Binding of estrogen to receptors on melanocyte and keratinocytes can activate tyrosinase and MITF pathways
- ▶ increased PDZK1 expression in melasma mediate interaction between estrogen and ion exchanger to increase melanogenesis and melanosome transfer

Pathogenesis & Pathology

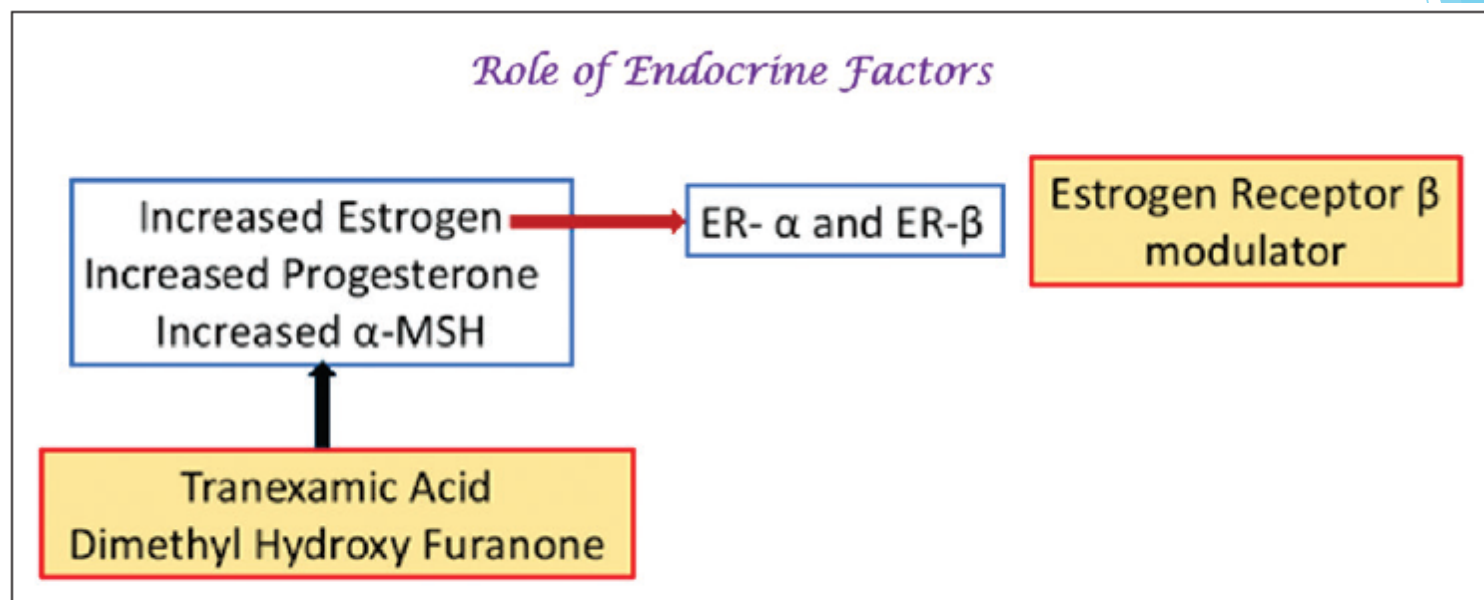


Figure 6: Summary of the various new drugs and their mechanism of action. 1–7 represent the mechanisms of development of melasma: 1 – hyperactive melanocytes and melanogenesis; 2 – melanosomal transfer to keratinocytes; 3 – inflammation and reactive oxygen species; 4 – skin barrier; 5 – dermal vasculature; 6 – mast cells and histamine; 7 – estrogen receptors. ER: estrogen receptors, NCAP: N-acetyl-4-S-cysteaminylphenol, TXA: tranexamic acid

Pathogenesis & Pathology

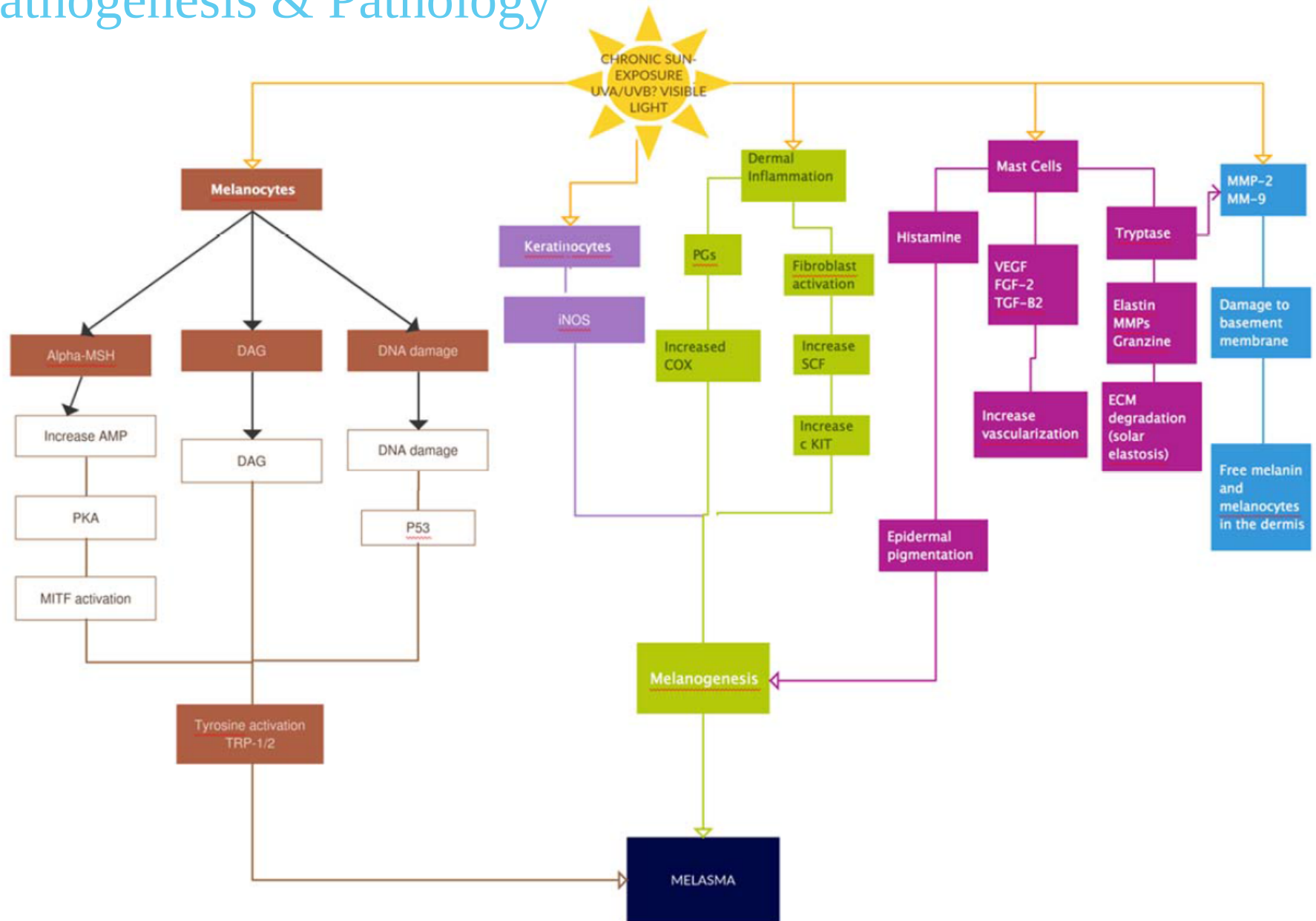


Figure 1. Flow diagram showing the total number of mobile apps found from the Apple App Store and the number of apps excluded from analysis (including reason for removal).

Treatment

Sunscreens

- ▶ Visible light → production of ROS and DNA damage
- ▶ Broad-spectrum UVA/UVB SPF30
- ▶ physical blocking agent preferred
 - ❖ Zinc oxide
 - ❖ Titanium dioxide
 - ❖ Iron-oxide against VL
- ▶ infrared light → activation of endothelin receptor B and have been role in melanogenesis
- ▶ systemic antioxidant :
 - ❖ Vitamin A, C, and E
 - ❖ Beta-carotene
 - ❖ Carotenoids

Treatment

Table 1. *Melasma pathogenesis and corresponding medical/experimental therapies*

Component	Mechanism of pathogenesis	Therapies	Level of Evidence	Reference
Tyrosine activation	Increases melanogenesis	Hydroquinone Azelaic Acid Glycolic acid siRNA agents Combination creams (*includes retinoid and steroid) Proton-pump inhibitors (block copper acquisition by tyrosinase, which leads to its degradation)	2a 1b 2b 2b 1b <i>Proposed therapy</i>	Ennes et al. [31] Balina LM and Graupe K [32] Sarkar et al. [33] Xiang Y et al. [27] Nordlund et al. [34] Matsui MS et al. [29]
UVB-induced Keratinocyte stimulation	Increases melanocyte production	Retinoids	1a	Griffiths CE et al. [35]
Neovascularization	Growth-factor induced angiogenesis	Tranexamic acid	1b	Atefi et al. [25]
cAMP accumulation and CREB phosphorylation	Controls downstream melanin synthesis pathways	Metformin	<i>Proposed therapy</i>	Lehraiki et al. [28]
Hormonal influence	Binding of estrogen activates downstream melanogenesis pathways	Estrogen antagonist	<i>Proposed therapy</i>	Cohen PR [21]

Treatment

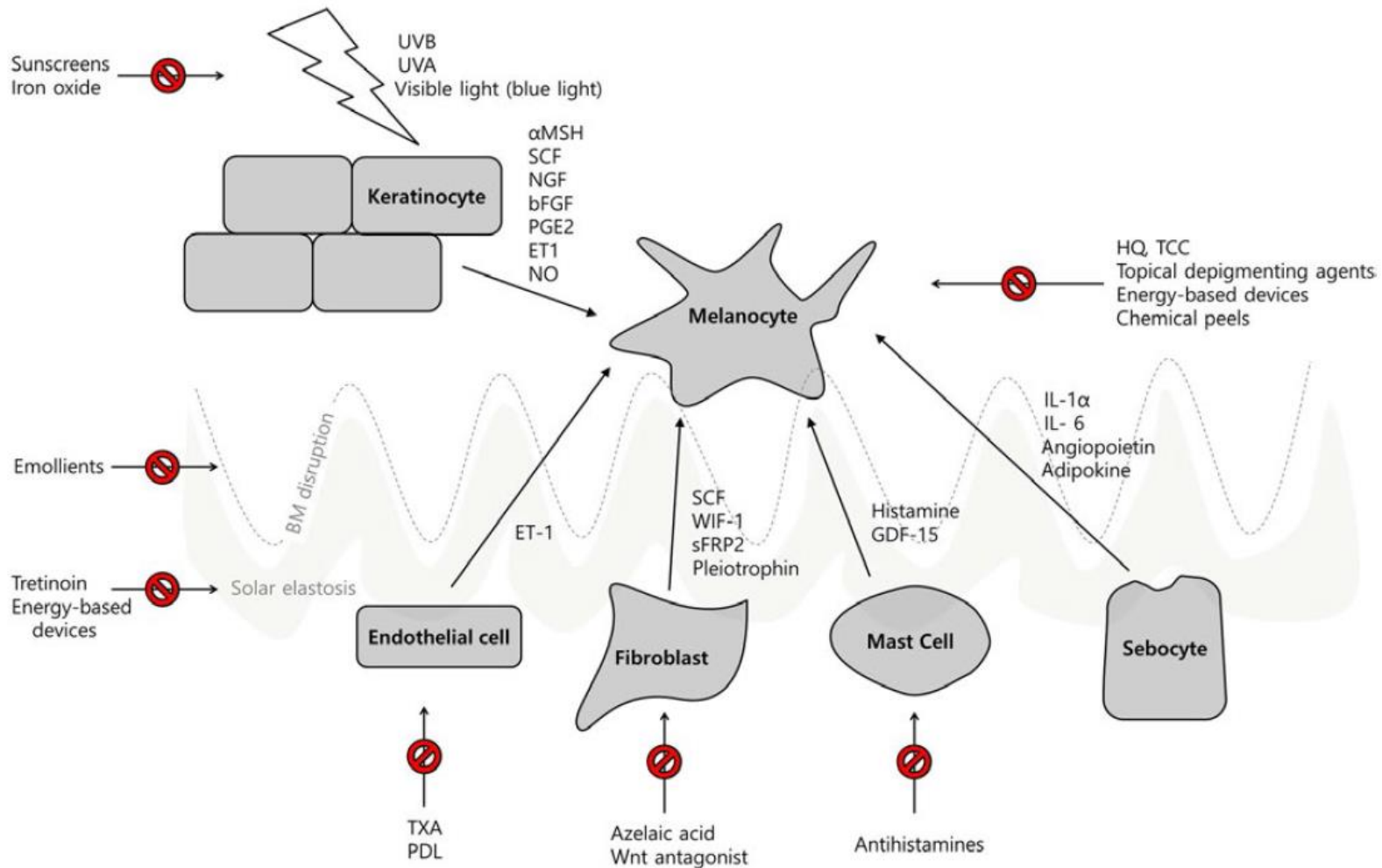


Figure 2-Schematic view of pathogenesis and therapeutic options of melasma.

Treatment

Target hyperactive melanocytes

- ▶ Linoleic acid (topical)
 - ❖ Tyrosinase inhibiting
 - ❖ Photoprotective
- ▶ Ascorbic acid (topical)
- ▶ N-acetyl-4-S-cysteaminylphenol (topical)
 - ❖ Tyrosinase inhibition

Treatment

Targeting Melanogenesis

- ▶ Hydroquinone (topical)
- ▶ Steroid (topical)
- ▶ Arbutin and deoxyarbutin (topical)
- ▶ Aloesin (topical)
- ▶ Rucinol (topical)
- ▶ Flavonoids (topical)
- ▶ Ellagic acid (topical)
- ▶ Gentisic acid (topical)

Treatment

Targeting melanogenesis...

- ▶ Hydroxycoumarins (topical)
- ▶ Cinnamic acid (topical)
- ▶ Antisense oligonucleotides (topical)
- ▶ Metformin (oral)
- ▶ Omeprazole (topical)
- ▶ Cardamonin & fingolimod (topical)
 - ❖ Inhibitor tyrosinase activity

Treatment

Target ROS and inflammation

- ▶ Liquorice extract (topical)
- ▶ Proanthocyanidin (oral)
- ▶ Acidified amino acid peeling (topical)
- ▶ Orchid extract (topical)
- ▶ Coffeeberry extract (topical)
- ▶ Mulberry extract (topical)
- ▶ Pycnogenol (oral)
- ▶ Vit C (oral)
- ▶ Vit E (oral)
- ▶ Azelaic Acid (topical)
 - ❖ Activation of PPAR- γ , inhibitor MMP, SCF

Treatment

Target Melanosomal Transfer

- ▶ Niacinamide (topical)
- ▶ Liquirtin (topical)
- ▶ Soymilk, soybean (topical)

Treatment

Target Defective Barrier

- ▶ Soy (topical)

Treatment

Target Vascular Component

- ▶ Tranexamic acid (oral)
 - ❖ 250 mg three times for 8 weeks
 - ❖ Topical can be asod

Treatment

Target Mast Cells

- ▶ Tranexamic acid (oral)
- ▶ Zinc (topical)
 - ❖ Inhibit mast cell degranulation

Treatment

Target Hormones

- ▶ Flutamide Topical
- ▶ Other estrogen receptor modulate
 - ❖ Tamoxifen
- ▶ aromatase inhibitor
 - ❖ Anastrozole

Treatment

Target Photoaging

- ▶ Tritinoein (topical)
- ▶ AHA (topical)

Other new treatment

- ▶ Curcumin (topical)
- ▶ Lignin peroxidase (topical)

Treatment

Procedural treatment

Platelet-rich plasma (PRP)

- ▶ TGF- β 1 released from α -granules
- ▶ Inhibition melanin synthesis
- ▶ Growth factor (GF) increase skin volume as a result of angiogenesis and synthesis of collagen

Treatment

Microneedling

- ▶ Enhancing drug delivery
- ▶ Two sessions, 1 month apart
- ▶ Combined with topical agent

Treatment

Peeling

- ▶ Controlled epidermal dyscohesion and subsequent regeneration
- ▶ Epidermal melanin removal
- ▶ unsatisfactory in skin types III–IV

Treatment

Laser

- ▶ IPL
- ▶ PDL
- ▶ fractional 1550-nm non-ablative laser
- ▶ Q-switched neodymium-doped yttrium laser
- ▶ Laser-toning 1064-nm QSNYL low fluence
 - ❖ Remove melanosomes and damage dendrites without destructing melanocytes
 - ❖ subcellular selective photothermolysis
- ▶ HIFU 1.5-mm transducer
 - ❖ As delivered under DEJ and eliminate melanin
 - ❖ Collagen denaturation and remodeling improve photoaging
- ▶ High intervisty laser degrade Basement membrane and allow descent of melanin to dermis

Treatment

Others

- ▶ Glutathione
 - ❖ Parenteral: not safe
 - Only in hepatic failure and chemotherapy neurotoxicity
 - ❖ Oral: safe
 - ❖ Topical: safe
- ▶ Little convincing evidence
- ▶ Many unresolved controversy
- ▶ Long term efficacy remain questionable

Treatment

Current Combination

- ▶ Anti Aging
- ▶ Hydroquinone
- ▶ tranexamic acid
- ▶ Lasers

Future Combination

- ▶ Hydroquinone
- ▶ Anti-estrogen receptor
- ▶ VEGF inhibitor
- ▶ Laser

THANKS

