ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 02 | February - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

REVIEW ARTICLE ON TREATMENT OPTIONS FOR MELASMA

Dermatology

Dr. M. Ravali* (Junior Resident), Department of Dermatology, Chettinad Hospital And Research Institute, Kelambakkam, TN, India. *Corresponding Author

Dr. P. Pavithra (Junior Resident), Department of Dermatology, Chettinad Hospital And Research Institute, Kelambakkam, TN, India.

Dr. Jayakar Thomas (HOD), Department of Dermatology, Chettinad Hospital And Research Institute, Kelambakkam, TN, India.

KEYWORDS

INTRODUCTION:

Melasma is an acquired ,chronic pigmentary disorder that predominantly is seen over the sun exposed areas of the face[1]. It can be regarded as a dysfunction in human melanogenesis [2] and results from increased activity of melanocytes [3], increased melanocytes, melanin, melanosomes and increase in synthesis of tyrosinase[4].

It presents as hyperpigmented patches or in different patterns like confetti macules ,large or linear patches with irregular ,serrated or geographic borders [5]. It can occasionally affect the V neck area and the forearms.

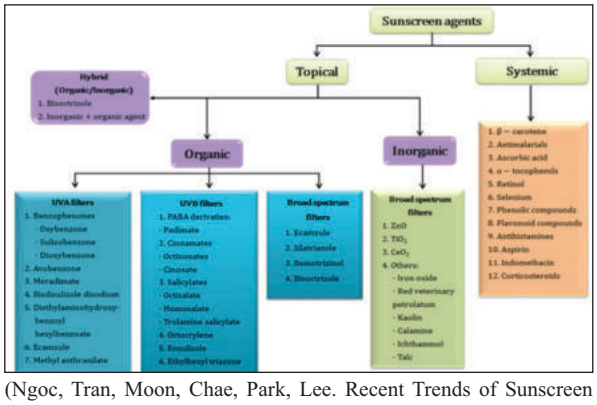
Treatment:

A) Prevention

UV rays protection and Sunscreens: [6]

Melasma being a pigmentary disorder occurring in sun exposed areas, strict photoprotection is mandatory. Sunscreens serve as the keystone in the management of Melasma.

Classification:



(Ngoc, Tran, Moon, Chae, Park, Lee. Recent Trends of Sunscreen Cosmetic: An Update Review. Cosmetics. 2019;6(4):64.)

Based on UV filters :

1) Organic Sunscreens (chemical):

They absorb UV rays and move on from a lower energy to higher energy.
It dissipates energy in the form of heat.
Eg: Octinoxate, Octisalate

2) Inorganic Sunscreens (physical):

They absorb, scatter and reflect UV rays.
They are opaque and produce a whitening effect of the formulation.
Eg: Zinc oxide, Titanium dioxide

Systemic photoprotective agents:

These are compounds with a systemic photoprotection.
Eg: Antimalarials, β-carotene, Vitamins (like A, C, and E), ascorbic acids, aspirin, antihistamines, aspirin, indomethacin, corticosteroids.

Polypodium leucotomos : It is a fern belonging to the family of Polypodiaceae present in Southern America. PL's can be used as an adjunct agent in melasma with photoprotective properties.

Mechanism of action :

- Blocking UV -induced COX-2 expression.
- Upregulates p53 suppressor gene expression.
- Promotes antioxidant systems endogenously.
- Modulates inflammatory cytokines.

B) Medical Management

Topical Agents

1) Hydroquinone (hq):

It is a white colored, odorless, substance with a very low vapor pressure and is highly soluble in alcohol.It is most widely prescribed and used as a skin lightening or depigmenting or bleaching agent. It is a gold standard agent for the treatment of Melasma and a prototype for pigmentary disorders. The most used concentration is 2% but higher (3-10%) concentrations are prescription products and should be used judiciously [7].

Mechanism Of Action: HQ acts by inhibition of Tyrosinase which is a rate limiting enzyme in melanin synthesis. This results in the inhibition of conversion of DOPA to melanin. It can also cause apoptosis melanocytes [8].

Side effects: [9]

Exogenous ochronosis, Erythema, Irritation, Colloid milium, Impaired wound healing, Leukoderma, Guttate hypomelanosis

2) Triple Combination:

Triple combination cream or Kligman's formula is one of the most widely used topical therapies in the management of melasma.This original formula was developed by Kligman-Wilis in the year 1975. They combined a 0.1% tretinoin, a mild steroid dexamethasone 0.1% and 5% hydroquinone. This initial preparation has been modified over the years.In India the recent modification is a combination of 2% hydroquinone, 0.1% mometasone, and 0.025% tretinoin [10]. Mometasone being a potent corticosteroid, can be tried for moderate to severe localised dermatological conditions. As it is more lipophilic, it can remain in high concentrations in the skin with less absorption occurring systemically [11].

Mechanism of action:

Tretinoin:

It enhances epidermal penetration by exerting a keratolytic action. It can also help prevent oxidation of Hydroquinone and can decrease chances of atrophy due to steroids.

Hydroquinone:

Depigmenting or bleaching agent that causes reduction pigmentation by inhibiting tyrosinase.

Corticosteroid:

Inhibits melanogenesis and decreases irritation caused by tretinoin and hydroquinone.

Modifications of triple combination:

1) Modified Kligman's regimens:

- 0.05% tretinoin, 4% HQ, and 1% hydrocortisone acetate.
- 0.025% tretinoin, 2% HQ, and 0.1% mometasone.
- 0.05% tretinoin,4% HQ, and 0.01% fluocinolone acetonide.

2) Pathak's formula which contains 0.05-0.1% tretinoin and 2% HQ
3) Westerhof's formula contains 0.1% triamcinolone acetonide, 4.7% N-acetylcysteine and 2% HQ.
4) Katsambas's formula : tretinoin 0.05%,HQ 4%, hydrocortisone acetate 1%

3) Other Topical Modalities :

Table-1 : Mechanism Of Action Of Various Topical Agents(Sarkar R, Chugh S, Garg VK. Newer and upcoming therapies for melasma. Indian J Dermatol Venereol Leprol 2012;78:417-428)

MOA	Agents
Competitive inhibition of Tyrosinase	Hydroquinone, Arbutin, Azelaic acid, Aloesin, Flavonoids, Kojic acid, Yohimbine, Seporin
Non competitive inhibition of Tyrosinase	Hydroxystilbenes, mulberry,Glabridin
Newer tyrosinase inhibitors	Diaryl propane
Reduction of Tyrosinase oxidation	P Coumaric acid
Reduction in melanin transfer	Soy, Niacinamide
Inhibition of melanocyte proliferation	Ellagic acid, Ascorbic acid
Facilitation of rapid pigment loss, removes keratinocytes.	Liquirtin, Retinoids

Kojic Acid:
Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyrone) is a fungal metabolite which is a naturally occurring compound derived from Penicillium, Acinetobacter and Aspergillus species. It is available as 1-4% in cream base and can be used as a monotherapy or in combination with several other topicals with a relatively good safety profile. Several studies showed that combination therapy with HQ can give a better outcome in melasma in Caucasians and Asians.It can be opted if a patient is intolerant towards other first line topical agents [12,13]

Mechanism of action: [14]
- Chelation of the free portion of tyrosinase
- Potent antioxidant
- Photoprotection

Side effects:
Erythema, Contact dermatitis, Irritation

Azelaic Acid:
It is a Non phenolic, naturally occuring, dicarboxylic acid that is derived from Pityriasporum ovale. It is available as both gel and cream formulations.(1-4%)

Mechanism of action :
- Inhibition of Tyrosinase
- Reduction of DNA synthesis
- Direct toxic effects on melanocytes.
- Decreases free radicals production. (Free radicals can lead to increased pigmentation) [15]

Azelaic acid cannot cause depigmentation in normal or nonlesional skin due to its action being limited only to abnormal and hyperactive melanocytes which also results in lesser side effects [9].

Side effects:
Stinging ,Pruritus, Erythema, Hypersensitivity

Arbutin:
It is a naturally occurring plant product and a derivative of Hydroquinone. It has been in use for the treatment of several pigmentary disorders.

Mechanism of action:
It is less toxic than hydroquinone as iTX action is dose dependent. It causes inhibition of tyrosinase,and thus decreases the formation of melanin. It can also have a role as a free radical scavenger but is less potent that hydrolysed Hydroquinone. Arbutin hydrolyzed by skin flora, possesses a much more potent free radical scavenging potential [15]. Deoxyarbutin, an arbutin derivative also has a role in skin lightening by causing reversible inhibition of Tyrosinase [14].

Retinoids:
Retinoids can cause an increase in the cell turnover and these changes can facilitate other skin lightening agents to penetrate into the epidermis resulting in an increase in skin lightening. Epidermopoiesis induced by retinoids can result in an enhanced loss of melanin. At concentrations of 0.05% to 0.1%, tretinoin can be used in the treatment of melasma but requires a long duration of 20 to 40 weeks.

Side effects:
- Burning
- Erythema
- Scaling
- Post inflammatory hyperpigmentation

Compared to tretinoin, Adapalene 0.1% as a monotherapy is safe and efficacious in melasma treatment [12].

Niacinamide:
It is a derivative of Niacin or Vitamin B3.

Mechanism of action:
- Reduction of melanosome transfer to the keratinocytes with no action on tyrosinase enzyme or proliferation of cells.
- Decreasing melanogenesis by disturbing the cell-signaling pathway between the melanocytes and keratinocytes.

Advantage: Heat and photostability.

Antioxidants:
1) Vitamin C:
Vitamin C or Ascorbic acid widely known for its photoprotective and antioxidant benefits is used in the treatment of several pigmentary disorders including melasma. It is available in various formulations ranging from 5 to 20% and can be used along with other depigmenting agents.

Disadvantages:
- Hydrophilic nature limits skin penetration.
- Chemical instability [12].

2) Melatonin:
Melatonin is a hormone secreted by the pineal gland. It is a potent antioxidant and a free radical scavenger. It can also stimulate several other enzymes with antioxidant properties like Glutathione reductase, Glutathione peroxidase, Superoxide dismutase etc. Besides the antioxidant property it can also decrease melanogenesis by inhibiting αMSH receptors and also progesterone and oestrogen [16].

Dose: Oral melatonin can be given up to a dose of 3mg/day for 3 months [17].

Side effects: Transient drowsiness

3) Glutathione:
Glutathione is a tripeptide of cysteine, glutamate and glycine. As it is produced by human cells it is known to be a very potent endogenous antioxidant. It is also being used widely by intravenous route for skin lightening [16].

Mechanism of action:
- Inhibition of tyrosinase
- Directing production of eumelanin to pheomelanin.

4) Pycnogenol:
It is an antioxidant and an anti-inflammatory agent extracted from the bark of a French pine named Pinus pinaster. It consists of procyanidins which have subunits of epicatechin and catechin, phenolic or cinnamic acids and polyphenolic monomers.

Mechanism of action:
- It scavenges free radicals and increases intracellular synthesis of antioxidant enzymes.
- Regeneration of Vitamin C and Vitamin E.

Advantage:
- High bioavailability

- Low incidence of side effects [18].

5) Zinc:
It has been widely used for pigmentary disorders for its anti-inflammatory, antioxidant properties.

Mechanism of action: [18]
- Reduces melanin production.
- Exfoliation and peeling activity.

Tranexamic Acid:
Introduction:
Tranexamic acid is a plasmin inhibitor, which is widely used as a hemostatic agent. It controls fibrinolysis and prevents abnormal excessive bleeding.Its use in melasma was accidentally discovered by Nijo Sadako in 1979 when he tried its use on a chronic urticaria patient. TXA can be used as a skin-lightening agent,by different routes like Oral, topical and intradermal [19].

Mechanism Of Action:
Prevention of the conversion of plasminogen to plasmin is the main action of Tranexamic acid. Other actions in melasma include reduction of UV rays induced melanogenesis and decreasing angiogenic factors hence causing reduction in vascularity.

Role of UV rays in melanogenesis:
UV rays can cause increased production of plasmin due to increase in the production of plasminogen activator by the keratinocytes.Action is through both direct and indirect effects which result in the upregulation of melanogenesis. Indirect effect is due to the production of various peptides like α-MSH and ACTH and cytokines by the sun damaged keratinocytes. Direct effect is due to increase in melanocyte proliferation and by stimulating melanogenesis.

TXA has its action only on lesional skin and it does not act on normal skin. It binds reversibly to plasminogen and thereby resulting in prevention of the interaction of plasmin with plasminogen. Upon being activated, p53 binds to Propiomelanicortin (POMC) and is later cleaved to α-MSH, γ-MSH, ACTH.

The α-MSH ⇒ acts on MCR-1 (on keratinocytes)⇒ Adenyl Cyclase activation and production of cAMP ⇒ Activation of Protein kinase A ⇒ phosphorylation of CAMP and CREB ⇒Upregulation of MITF Eumelanin production ⇒TXA causes downregulation of MITF thus reducing the production of Eumelanin.

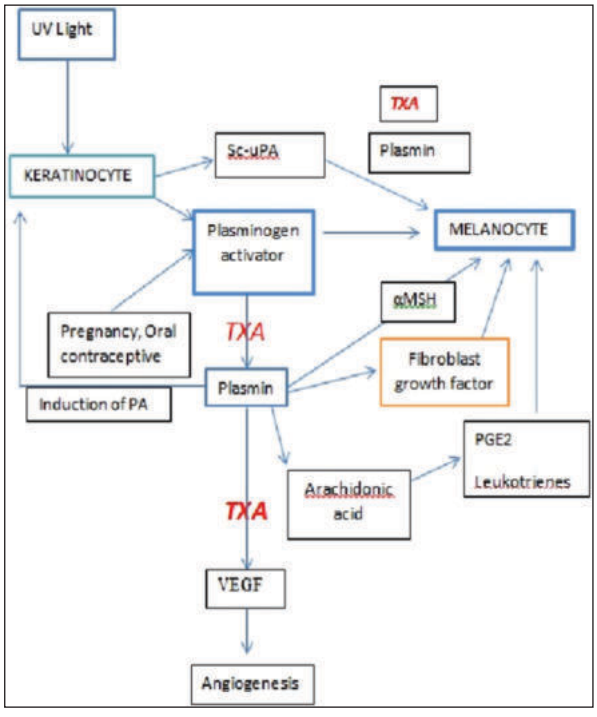


Figure 2⇒Mechanismb Of Action Of Txa (Poojary S, Minni K. Tranexamic Acid in Melasma: A Review. Journal of Pigmentary Disorders. 2015;2(12).)

Release of PGE2:
Plasmin ⇒ stimulates phospholipase ⇒Cleaves glycerophospholipid Arachidonic acid(AA)PG's and LT'sLT'sStimulate Melanogenesis and Angiogenesis [20].

Intradermal TXA:
The highly resistant to treatment forms like dermal and mixed variants justify the use of TXA intradermally.

Availability: 5 mL ampoule containing 500 mg of the drug [21].

Side effects: [20]

Oral TXA: Oligomenorrhea, Palpitations, Nausea, Diarrhoea, Venous- thromboembolism, Pulmonary embolism Topical TXA – Stinging ,erythema, - xerosis, burning Intradermal– edema, pain , irritation, burning.

C) Chemical Peels:
It is controlled destruction of layers of the skin (epidermis or dermis) by application of a chemical substance which is later followed by remodelling and regeneration of the tissues as a part of healing [22]. Glycolic acid, Tretinoin, Salicylic acid, Mandelic acid and Jessner's peel are commonly used for melasma.

Peels can also be used as combination therapy with other procedural treatments like lasers, microneedling or with other topical agents.

Classification Of Peels: [23]
- Very Superficial light peels : Necrosis occurs upto stratum corneum only. Agents: TCA peel 10%, GA peel 30-50%, Tretinoin 1-5%, Salicylic acid peel 20-30%, Jessner's solution (1-3 coats)
- Superficial light peels : The entire epidermis up to basal layer is necrosed. Agents used: TCA peel 10-30%, Jessner's solution (4-7 coats), GA peel 50-70%
- Medium depth peels : Necrosis occurs involving the upper reticular dermis.
- Agents used: TCA peel 35-50%,88% phenol, GA peel 70% + TCA 35%, solid CO 2 + TCA 35%.
- Deep peels : Necrosis occurs until the mid-reticular dermis. Agents used: Baker-Gordon phenol peel

Mechanism Of Action:
- SALICYLIC ACID peel: It is a keratolytic. It is best suited for oily skin due to its lipophilic nature. Excess application can lead to Salicylism due to systemic absorption.
- AHA peel: Causes desquamation and peeling by acting on epidermal cohesion enzymes.
- RETINOIC ACID: Keratolytic effect by binding to the receptor RAR or RXR.
- TCA peel: It has a caustic effect by causing coagulation of proteins.
- PHENOL peel: Cell death by causing protein denaturation, enzyme inactivation and increased cell permeability.

Contraindications:
Unrealistic expectations, active infections, pre existing dermatosis, keloidal tendency, photosensitivity, hypersensitivity, cardiac or renal diseases, pregnancy

D) Lasers: [24]
Lasers are generally opted as the last resort or third line treatment for melasma if there is no considerable response to other modes of treatment. It gives best results on combining with other topical agents or peels. Due to a higher risk of PIH in dark skinned individuals it has to be used with great caution.

The lasers for use in melasma are: Pulsed CO2 laser, PDL (500-520nm), Intense Pulsed Light (IPL), Copper bromide lasers (511nm), Erbium:YAG (2940nm), Q-switched ruby (694nm), Q-switched Nd:YAG (532nm and 1064nm) and Q-switched alexandrite laser (755nm)

Principle:
Lasers work on the principle of photothermolysis in melasma. When a time lesser than that of the Thermal relaxation time of a specific target tissue is chosen, the energy of a specific wavelength will be restricted

to the tissue targeted and causes less damage to the surrounding tissue. Therefore an appropriate wavelength for that particular target (chromophore) should be emitted by a laser. For example, for melanin, the wavelength selected is 630 nm -1,100 nm. If the wavelength is longer, the penetration will be deeper resulting in more damage.

E) Camouflage:

Cosmetic camouflage is tried when all modes of treatment have failed and when the lesions are extremely resistant to treatment. It is done by concealment of discoloration of the skin with the help of makeup. This can also be used in the concealment of scars, papules, nodules, small or large areas of hypo or hyperpigmentation. It can be either temporary or permanent(tattooing) [25].

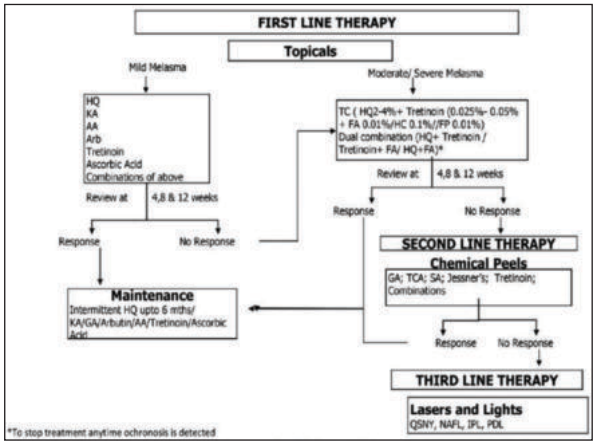


Figure 3: Treatment Algorithm Of Melasma (Sarkar R, Gokhale N, Godse K, Ailawadi P, Arya L, Sarma N et al. Medical management of melasma: A review with consensus recommendations by Indian pigmentary expert group. Indian Journal of Dermatology. 2017; 62(6): 450.)

REFERENCES:

1. Young Kang H, Ortonne J. Melasma Update. Actas Dermo-Sifiliográficas. 2009;100:110-113.
2. Handel AC, Miot LD, Miot HA. Melasma: a clinical and epidemiological review. *An Bras Dermatol*. 2014;89(5):771-782.
3. Miot LD, Miot HA, Silva MG, Marques ME. Fisiopatologia do melasma [Physiopathology of melasma]. An Bras Dermatol. 2009 Nov-Dec;84(6):623-35.
4. Victor FC, Gelber J, Rao B. Melasma: a review. J Cutan Med Surg. 2004 Mar-Apr;8(2):97-102. doi: 10.1007/s10227-004-0158-9. Epub 2004 May 4. PMID: 15685388.
5. Bandyopadhyay D. Topical treatment of melasma. Indian J Dermatol 2009;54:303-9.
6. Kaimal S, Abraham A. Sunscreens. Indian J Dermatol Venereol Leprol 2011;77:238-243.
7. Hydroquinone.S.C. Gad, T. Pham, in Encyclopedia of Toxicology (Third Edition), 2014.
8. Sarkar R, Gokhale N, Godse K, Ailawadi P, Arya L, Sarma N, Torsekar R G, Somani V K, Arora P, Majid I, Ravichandran G, Singh M, Aurangabadkar S, Arsiwala S, Sonthalia S, Salim T, Shah S. Medical management of melasma: A review with consensus recommendations by Indian pigmentary expert group. Indian J Dermatol 2017;62:558-77.
9. Chatterjee M, Vasudevan B. Recent advances in melasma. Pigment Int 2014;1:70-80.
10. Majid I. Mometasone-based triple combination therapy in melasma: is it really safe?. *Indian J Dermatol*. 2010;55(4):359-362.
11. Godse KV. Triple combination of hydroquinone, tretinoin and mometasone furoate with glycolic acid peels in melasma. *Indian J Dermatol*. 2009;54(1):92-93.
12. Damevska, Katerina. "New Aspects of Melasma/Novi aspekti melazme" Serbian Journal of Dermatology and Venereology, vol.6, no.1, 2014, pp.5-18.
13. Davis EC, Callender VD. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. *J Clin Aesthet Dermatol*. 2010;3(7):20-31.
14. Chatterjee M, Vasudevan B. Recent advances in melasma. Pigment Int 2014;1:70-8.
15. Bandyopadhyay D. Topical treatment of melasma. Indian J Dermatol 2009;54:303-9.
16. Grimes P, Ijaz S, Nashawati R, Kwak D. New oral and topical approaches for the treatment of melasma. International Journal of Women's Dermatology. 2019;5(1):30-36.
17. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, BulengoRansby SM, Ellis CN, et al. Topical retinoic acid (tretinoin) for melasma in black patients. A vehicle-controlled clinical trial. Arch Dermatol. 1994; 130: 727-3.
18. Sarkar R, Chugh S, Garg VK. Newer and upcoming therapies for melasma. Indian J Dermatol Venereol Leprol 2012;78:417-428.
19. Feng, X., Su, H. and Xie, J. (2021), Efficacy and safety of tranexamic acid in the treatment of adult melasma: An updated meta-analysis of randomized controlled trials. J Clin Pharm Ther, 46: 1263-1273.
20. Soundarya S, Srinivasan M. TRANEXAMIC ACID IN DERMATOLOGY. Annals of Tropical Medicine and Public Health. 2020;23(15).
21. George, Anju. (2016). Tranexamic acid: An emerging depigmenting agent. Pigment International. 3. 66. 10.4103/2349-5847.196295.
22. Brody H. History of chemical peels. In: Baxter S, editor. Chemical peeling and resurfacing. 2nd ed. St. Louis: Mosby Year Book Inc; 1997. p. 1-5.
23. Savant SS. Superficial and medium depth chemical peeling. In: Textbook of dermatosurgery and cosmetology. In: Savant SS, editor. 2nd ed. ASCAD; 2005. p. 177-95.
24. Sarkar R, Aurangabadkar S, Salim T, Das A, Shah S, Majid I, Singh M, Ravichandran G, Godse K, Arsiwala S, Arya L, Gokhale N, Sarma N, Torsekar R G, Sonthalia S, Somani V K. Lasers in melasma: A review with consensus recommendations by Indian pigmentary expert group. Indian J Dermatol 2017;62:585-90.
25. Kaliyadan F, Kumar A. Camouflage for patients with vitiligo. Indian J DermatolVenereolLeprol 2012;78:8-15.