SEMINAR PRESENTATION

TREATMENT OF MELASMA

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Melasma

- Acquired pigmentary disorder that occurs mainly in women (more than 90% of cases) of all racial and ethnic groups, but particularly affects those with Fitzpatrick skin types IV–VI
- Acquired bilateral symmetrical hypermelonosis
- Irregular light to gray brown macule and patch
- Ill defined margin
- Involved sun exposure area
- **Distribution of melasma-**

- Central facial pattern (63%) : cheek, forehead, nose, chin
- Malar pattern (21%) : cheek, nose
- Mandibular pattern (16%) :chin

- **Cause of melasma-**
- Exact cause unknown
- Light : UVA, UVB, visible light : cause peroxidation of lipids in cellular membranes, leading to generation of free radicals, which stimulate melanogenesis.
- Elevated levels of estrogens and progesterone- pregnancy, contraceptive pill, HRT
- Thyroid disease
- Drug : dilantin, anti-malarial drug, tetracycline, minocycline
- Cosmetic : perfume, color
- Genetic: >30% have a family history of melasma.
- Malnutrition : liver dysfunction, B12 def.

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PATHOGENESIS

I. Number of melanocytes in the lesions may be normal or increased.
II. Melanosomes both within melanocytes and keratinocytes are increased in size.
III. Increased expression of α-MSH in keratinocytes and overexpression of stem cell factor in fibroblasts and its receptor C-kit in melanocytes of involved skin.

Type of melasma

- Epidermal melasma-
- Light or dark brown color
- Melanin deposition in basal, suprabasal layer of epidermis
- Larger melanocyte with more noticeable dendritic process
- Dermal melasma-
- Blue gray color
- Perivascular melanophage at superficial and middermis
- Melanin granule in dermis
- Mixed epidermal dermal melasma

- Face is most commonly affected.
- Rarely pigmentation may extend on to V of the neck or may be confined to the forearms.
- On the face, three patterns of melasma are recognized:

A. ***Centrofacial:*** the most frequent (63%) pattern, with pigmentation on cheeks, forehead, upper lip, nose, and chin.
B. ***Malar:*** constituting 21%, with pigmentation present only on cheeks and nose.
C. ***Mandibular:*** the least common (16%), with pigmentation on ramus of the mandible.

COURSE

- Depending on the natural history of the lesions, melasma may also be classified into:

a. ***Transient type:*** which disappears within a year of withdrawal of hormonal stimulus.

b. ***Persistent type*** : which persists for more than a year after withdrawal of hormonal stimulus and is maintained by UVR and other factors.

Evaluating melasma- MASI and PGA

- The Melasma Area Severity Index (MASI) evaluates the severity of the melasma in each of the four regions,
  - ✓ forehead (30%)
  - ✓ right malar region (30%)
  - ✓ left malar region (30%)
  - ✓ chin (10%),
- Based on three variables:

a) percentage of the total area involved (A),
b) darkness of the macules (D)
c) homogeneity (H).

- The scored range is from 0 to 48.

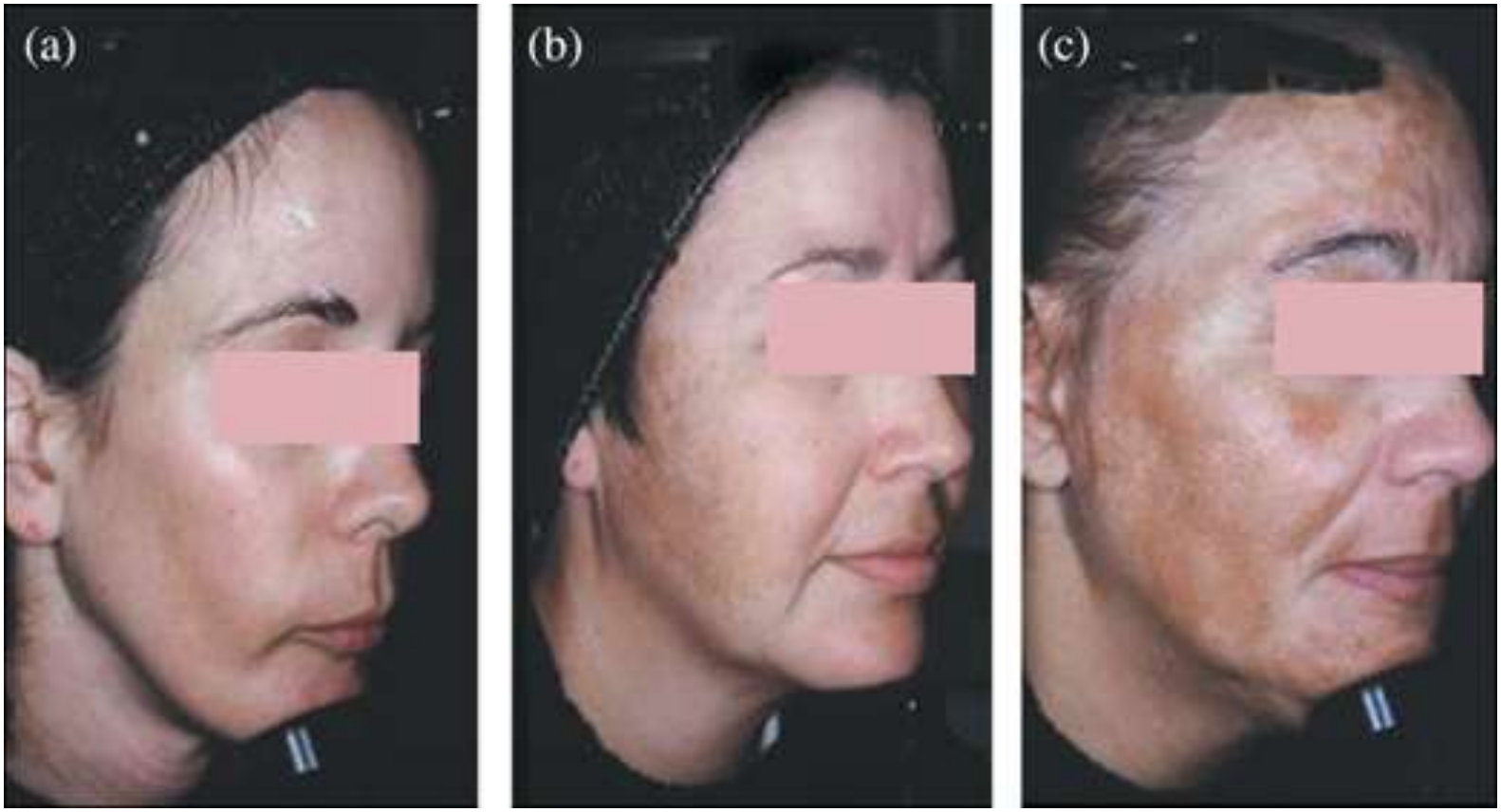

Figure 1 Melasma: (a) mild, (b) moderate, (c) severe.

Treatment of melasma

Topical hypopigmenting

- Sunscreens
- Hydroquinone (HQ),
- Tretinoin (RA),
- Kojic acid, and
- Azelaic acid

Physical therapies-

- Chemical peels
- Glycolic acid [GA],
- Trichloroacetic acid [TCA]

laser therapy and

- pulsed CO2 laser
- Q-switched alexandrite laser.

TOPICAL THERAPIES

Sunscreens-

- Patients should be educated on the use of daily broad spectrum sunscreen with a sun protection factor (SPF) of 30 and sun-protective measures, such as avoidance and protective clothing.
- Sunscreens containing physical blockers, such as titanium dioxide and zinc oxide, are preferred over chemical blockers because of their broader protection
- Although clinical studies have shown that serum vitamin D levels are reduced in sunscreen users compared to nonusers, these levels are still within normal range.

Hydroquinone

- Inhibits tyrosinase.
- Other proposed mechanisms- inhibition of DNA and RNA synthesis, degradation of melanosomes, and destruction of melanocytes.
- Can cause permanent depigmentation when used at high concentrations for a long period of time.
- Used at concentrations 2% - 5%,
- Adverse effects- irritant dermatitis, contact dermatitis, postinflammatory pigmentation, ochronosis, and nail bleaching

- Ennes et al. reported on the use of HQ 4% in a double-blind, placebo controlled trial involving 48 patients
- Both applied twice daily for 12 weeks; both contained a sunscreen with a SPF of 30.
- Results- HQ group total improvement- 38%, Partial improvement and no treatment failures-57%, and 5% Discontinued therapy
- Placebo group- total improvement- 8%, partial improvement- 58%, treatment failures- 17%
- Both therapies were well tolerated, with no serious adverse events reported.

- In a more recent placebo-controlled study, HQ 4% was compared with a skin whitening complex consisting of a mixture of-
- Uva ursi extract (a competitive inhibitor of tyrosinase that provokes chemical decoloration of melanin),
- Biofermented Aspergillus(chelates copper ion needed for tyrosinase activity),
- Grapefruit extract (exfoliative action), and
- Rice extract (hydrating function)
- In 30 patients over a 3-month period.

- Treatment evaluation consisted of patient questionnaires and two independent observers.
- According to the observer evaluations-
- HQ group-77% improvement with a 25% side-effect rate, primarily pruritus
- Skin-whitening complex- 67% improvement and 0% side effects

Retinoids

- **Tretinoin**-
- Inhibitory effect on tyrosinase by inhibiting the enzyme's transcription, as well as on dopachrome conversion factor, with a resulting interruption of melanin synthesis.
- Reduces hyperpigmentation through the induction of desquamation.
- Concentrations 0.05% to 0.1% have been used
- Side effects- erythema and peeling in the area of application; pIH.
- RA 0.1% has been used to treat melasma in 30 black patients, with results indicating that the average MASI score of the tretinoin-treated group decreased by 32% vs 10% from baseline in the vehicle control group.

- Histological examination of treated skin- significant decrease in epidermal pigmentation in the RA group compared with the control group.
- Another RCT of 0.1% RA once daily in 38 Caucasian women indicated that 13 of 19 tretinoin-treated patients (68%) were clinically rated as improved or much improved, compared with 1 of 19 patients (5%) in the vehicle group (P= .0006).
- Significant improvement first occurred after 24 weeks of tretinoin treatment.
- Colorimetry (an objective measure of skin color) demonstrated a 0.9 unit lightening of tretinoin-treated melasma and a 0.3 unit darkening with vehicle (P = .01).

Adapalene.

- Adapalene is a naphthoic acid derivative with potent retinoid activity; it controls cell proliferation and differentiation and has significant anti-inflammatory action.
- A randomized trial of 0.1% adapalene versus 0.05% tretinoin for 14 weeks in 30 Indian patients indicated a 41% and 37% reduction in MASI scores with adapalene and tretinoin, respectively (not significant).
- Side effects were significantly more frequent with tretinoin than with adapalene; 63% of patients treated with tretinoin suffered with pruritus, burning, dryness, erythema and scaling compared with mild erythema and a burning sensation in 8% and dryness in 13% of patients treated with adapalene.

Azelaic acid

- Naturally occurring as a dicarboxylic acid, isolate from the organism responsible for Pityriasis versicolor
- Antiproliferative and cytotoxic effects on melanocytes, which are mediated via inhibition of mitochondrial oxidoreductase activity and DNA synthesis.
- Weak competitive inhibitor of tyrosinase in vitro.
- Available as a cream at a concentration of 15% to 20%.
- A 20% azelaic acid based cream has been used to treat 39 patients for 6 months with two applications per day.
- Overall judgment of physician and patient were excellent or good in 79% and 85%, respectively.

- A randomized, doubleblind comparative study in 155 patients of Indo Malay-Hispanic origin found that 20% azelaic acid was superior to HQ 2%.
- Over a period of 24 weeks, 73% of the azelaic acid patients compared with 19% of the HQ patients had good to excellent overall results, as measured by the reduction of the pigmentary intensity of melasma and lesion size (P\.001).
- In a double-blind study by Balina and Graupe involving 329 women, 20% azelaic acid was shown to be as effective as HQ 4%, without the latter’s undesirable side-effects.

- In the azelaic acid treated patients, 65% of outcomes were graded as good or excellent compared with 72.5% of those of HQ-treated patients.
- Azelaic acid 20% plus tretinoin 0.05% or 0.1% has been shown to be more effective in enhancing the skin lightening effects of azelaic acid alone.
- In an open-label randomized study of 50 patients, 24 weeks of treatment with azelaic acid 20% and azelaic acid 20% plus tretinoin 0.05% resulted in excellent results in 5.3% and 34.8% of patients, respectively.

- Sarkar, Bhalla, and Kanwar16 have also studied sequential therapy of the potent topical steroid clobetasol propionate and azelaic acid.
- Thirty Indian patients with melasma had azelaic acid 20% applied to one half of the face twice daily for 24 weeks and to the other half, clobetasol propionate 0.05% for just 8 weeks followed by azelaic acid 20% for the remaining 16 weeks.
- Results showed no difference at 24 weeks in the lightening produced by either treatment; 96.7% and 90% of patients had good to excellent responses with azelaic acid plus steroid and azelaic acid, respectively

Niacinamide

- Niacinamide is the physiologically active derivative of vitamin B3 or niacin.
- In-vitro studies show that niacinamide significantly decreases melanosome transfer to keratinocytes without inhibiting tyrosinase activity or cell proliferation
- One of the advantages of niacinamide is its stability being unaffected by light, moisture, acids, alkalis, or oxidizers.
- Topical 2 to 5% niacinamide has shown some efficacy when used alone or in combination with N-acetyl glucosamine for the treatment of melasma and UV-induced hyperpigmentation in fair skinned patients and Asians.

Arbutin

- Arbutin is one of the most widely prescribed skin-lightening and de-pigmenting agent worldwide.
- Arbutin, the b-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant derived compound found in dried leaves of a number of different plant species including, bearberry, blueberry, cranberry and pear trees.
- Arbutin, inhibits tyrosinase activity competitively but at non-cytotoxic concentrations in a dose dependent manner in cultured melanocytes.
- It also inhibits melanosome maturation and is less cytotoxic to melanocytes than hydroquinone.
- Although, higher concentrations may be more efficacious, greater risk for paradoxical hyperpigmentation exists.
- Controlled trials on treating hyperpigmentation are lacking.

N-acetyl glucosamine

- *NAG is* an amino sugar that is a precursor to hyaluronic acid and is found throughout nature and human tissues.
- Its depigmenting ability originates from inhibition of tyrosinase glycosylation, a step necessary in production of melanin.
- It inhibits the conversion of pro-tyrosinase to tyrosinase and also affects the genes involved in hyperpigmentation.
- In a study conducted by Bessett, 2% NAG was found to reduce facial hyperpigmentation after 8 weeks of application.
- Its combination with niacinamide has been found to have greater de-pigmenting effect in various clinical studies.
- It is a component of various over-the-counter products used for hyperpigmentation.

Licorice extract

- Obtained from the root of Glycyrrhia Glabra Linnera.
- It is cultivated extensively in India.
- Licorice extract improves hyperpigmentation by dispersing the melanin, inhibition of melanin biosynthesis and inhibition of COX activity thereby decreasing free radical production.
- Glabridin, a polyphenolic flavonoid is the main component of licorice extract.
- One study conducted in 20 Egyptian women showed that topical liquiritin cream (1g/day) for four weeks was both safe and effective in the treatment of melasma.
- Further clinical studies are needed to evaluate the efficacy of licorice root extract in the treatment of PIH.

N-acetyl-4-S-cysteaminylphenol

- Phenolic and catecholic compounds are potent depigmenting agents of the skin.
- A retrospective observation of 12 patients treated with 4% N-acetyl-4-S-cysteaminylphenol, a tyrosinase substrate, showed a complete loss (8%), a marked improvement (66%), or a moderate improvement (25%) of melasma lesions.
- Visible changes in the melanin in the dermis were seen 2 to 4 weeks after daily topical application.
- This depigmentation was associated with a decrease in the number of functioning melanocytes and in the number of melanosomes transferred to keratinocytes.

RA plus HQ

- RA 0.1% plus 3% HQ has been evaluated in 40 female Korean women in a 20-week open label study.
- Overall, 59% of patients were rated as having excellent to good improvement by physician and patient evaluations after therapy.
- Majority of patients (96%) noted mild to moderate reactions to tretinoin cream.
- Sensations of burning, itching, erythema, and scaliness lessened with continued therapy.

GA plus HQ

- A study compared 10% GA + 4% HQ in a cream containing vitamins C and E and sunscreen with sunscreen alone.
- A total of 39 Hispanic women with Fitzpatrick skin types III-Vand bilateral epidermal melasma were enrolled in this randomized, controlled 12-week trial.
- Changes in pigmentation were measured by means of a Mexameter, the MASI, and a global evaluation by the patient and a blinded investigator.
- Results- significant decrease in the degree of pigmentation using the study cream compared with sunscreen alone;75% versus 13% of patients improved (P\.0001).
- Irritation was more common with the study cream

GA, HQ, or kojic acid

- Kojic acid, a compound derived form the fungus Aspergillus oryzae, has been shown to inhibit tyrosinase and has been studied in combination with other agents.
- GA 5% combined with either 4% HQ or 4% kojic acid daily for 3 months has been compared in a split-face design in 39 patients with melasma.
- Both combinations proved equally effective,with reduction of pigmentation in 51% of patients; dramatic results were noted in 28% of patients treated with GA/kojic acid and in 21% treated with GA/HQ.

Patients showing more than 50% improvement in melasma at the end of the study involving 12 weeks of treatment with kojic acid 2% gel plus glycolic acid 10% and hydroquinone 2% or glycolic acid 10% and hydroquinone 2%

Improvement in melasma	Kojic acid + GA + HQ	GA + HQ
<50%	16 (40.0%)	21 (52.5%)
>50%	24 (60.0%)	19 (47.5%)
Total	40 (100%)	40 (100%)

HQ, RA, and steroid combinations

- Addition of tretinoin 0.05% to 0.1% prevents the oxidation of HQ, as well as improving epidermal penetration, allowing pigment elimination and increasing keratinocyte proliferation.
- First proposed in 1975, Kligman's formula (KF; HQ 5%, tretinoin 0.1%, and dexamethasone 0.1%) has been the most widely used combination therapy for melasma worlwide.
- Addition of corticosteroids decrease irritative effects of the hypopigmenting agents, as well as inhibiting melanin synthesis by decreasing cellular metabolism.
- Tretinoin abrogate epidermal atrophy with topical corticosteroids.

- A triple fixed combination of HQ 4%, RA 0.05%, and FA 0.01% has been studied in 641 patients with moderate to severe melasma and Fitzpatrick skin types I to IV.
- Study compared the triple combination with HQ/RA, FA/RA, and FA/HQ over a period of 8 weeks; sunscreen with a sun protection factor of 30 was used in all patients.
- Complete clearing on or before day 56 was reported in 26.1%, 9.5%, 1.9%, and 3.1% of patients on a regimen of HQ/RA/FA, HQ/RA, FA/RA, and FA/HQ, respectively.
- Comparative results for percentages of cleared/almost cleared lesions were 77%, 46.8%, 27.3%, and 42.2%.
- Adverse events were mild to moderate; were erythema, skin peeling, burning, and/or stinging sensation.

- Forty Indian patients with Fitzpatrick skin types III to IV with moderate to severe melasma were randomized to treatment with the modified KF{HQ 2%} daily plus 6 serial GA treatments at 3-week intervals or to modified KF alone.
- A significant decrease in the MASI score at 21 weeks compared with baseline was observed in both groups.
- Group receiving GA showed a trend toward more rapid and greater improvements than the group only receiving the modified KF.
- At 12 weeks there was a 46% reduction and at 21 weeks an 80% reduction in MASI in the combined therapy group.
- This compared with a 33% and 63% reduction with KF alone at 12 and 21 weeks, respectively.

Oral antioxidants

- In a randomized, double bind, placebo-controlled trial, a combination of oral proanthocyanidin plus vitamin A, C, and E was assessed in 60 Phillipino females with bilateral epidermal melasma.
- Antioxidants were taken twice daily for 8 weeks and were compared with placebo intake by mexametric and MASI score analysis.
- There was significant reduction in MASI scores ($P = 0.001$)) and pigmentation by mexametry (P value < 0.0001) in malar regions.
- Combination was also well-tolerated.

Oral agents used topically

- Among the oral antioxidants, ascorbic acid is well-known for its efficacy as depigmenting agent. However, due to the unstable nature of vitamin C (rapid oxidation in aqueous solutions on topical application), a formulation containing 25% L ascorbic acid and chemical penetration enhancer was evaluated for efficacy and stability in melasma patients.
- 40 patients were treated in an open, uncontrolled trial with a commercial preparation applied topically for 16 weeks, and patients were assessed every 4 weeks using MASI and mexameter scoring There was significant decrease ($P < 0.05$) in the degree of pigmentation by both parameters, and also an improved quality of life was noted with decrease in melasQOL scores.

- Zinc is another oral antioxidant, antiinflammatory agent, which has been extensively studied in pigmentary disorders, which has peeling and exfoliating properties and reduces melanin production.
- Sharquie *et al* conducted an open clinical trial with 28 patients of melasma who applied Zn SO4 cream twice daily for 8 weeks and were followed for MASI scoring every 2 weeks till 3 months after stopping the treatment.
- There was 49.78% improvement in the mean MASI scores ($P < 0.005$), which was maintained at even 3 month follow-up visit.
- No side effects were noted, except mild burning sensation in few patients.
- Thus, zinc might serve as a new, effective, safe, non-costly formulation for melasma with long-lasting effects.

PHYSICAL THERAPIES

- **Chemical peels-**
- include such agents as GA, TCA, Jessner's solution (lactic acid, salicylic acid, resorcinol, and ethanol), salicylic acid, tretinoin, and kojic acid.
- GA peels 10% to 70% are popular
- 91% reduction in MASI score was found in a study involving 25 nonpregnant women treated with 50% GA once per month for 3 consecutive months.
- Patients enrolled had a minimum MASI score of 15 and those with epidermal type melasma had a better response to therapy than those with mixed-type melasma.
- One patient developed a mild degree of hyperpigmentation

- GA 70% has been compared with Jessner's solution in a split-face design trial with 16 patients.
- Colorimetric analysis showed an average lightening of 3.14 6 3.1 on the GA-treated side and 2.96 6 4.84 on the Jessner solution treated side (no statistical significance).
- Only adverse events reported occurred on the GA-treated area, crusting,PIH, and erythema.
- Follow-up of 5 patients at 16 months indicated that patients who continued topical therapy maintained their improvement, whereas those who discontinued experienced relapse.

- Addition of GA 20% to 30% to 4% HQ has been studied in 21 Hispanic women with bilateral epidermal and mixed melasma.
- Patients underwent twice-daily full-face application of HQ plus GA 20% to 30% to one side of the face only every 2 weeks and pigmentation was measured by means of a mexameter (spectrophotometric skin coloration measure of melanin and hemoglobin levels) and the MASI.
- Results indicated that both treatments significantly reduced (P \.001) skin pigmentation compared with baseline; however, no difference was observed between the two regimens

- Combination of 10% GA and 2% HQ has been studied in 10 Asian women with moderate to severe melasma.
- Combination therapy was applied twice daily to both sides of the face for 26 weeks and 20% GA peels to one side every 3 weeks (total of 8 peels).
- Assessment by a dermatologist was made using the Munsell color chart.
- Results indicated that with GA/HQ plus GA peel therapy up to 33% lightening of melasma was found in 6 patients and up to 66% lightening in 4 patients.

- With the GA/HQ therapy alone, 8 patients had lightening classified as slight (≤33%) in 7 patients and moderate (≤ 66% lightening) in 1 patient
- Salicylic acid 20% to 30% at 2-week intervals has been used in 25 dark-skinned patients (Fitzpatrick skin types V-VI), including 6 with melasma, with good results.
- Five peelings were conducted in patients previously treated with 4% HQ for 2 weeks and resulted in moderate to significant improvement in 88% of patients.
- Minimal to mild side effects occurred in 16%

- Concentrations of 1% to 5% RA have been evaluated in a skin peeling protocol in 15 women with melasma and photoaged skin with Fitzpatrick skin types I to IV.
- There was a clinical improvement in skin texture and appearance after 5 sessions of treatment applied at 2- to 3-day intervals.
- Histological examination before and after treatment revealed a decrease in the corneal layer, an increase in the epidermal thickness, and a lengthening of the cristae cutis (skin ridges).
- A chemical peel protocol involving GA 50% plus kojic acid 10% has been evaluated in 20 patients with diffuse melasma
- Treatment was applied at 2-week intervals for 3 to 6 months

- Complete regression was observed in 6 patients (30%), partial regression in 12 (60%), and no regression in 2 (10%).
- In a comparative study of 40 Chinese women with epidermal melasma, half of the face was treated with kojic acid 2% gel plus GA 10% and HQ 2% and the other half of the face with the same preparation but without the kojic acid twice daily for 12 weeks.
- 23 Of the patients treated with combination therapy, clearing of melasma was reported in 60% compared with 47.5% receiving GA/HQ.
- Side effects included erythema, redness, stinging, and exfoliation, which occurred on both sides of the face but resolved by the third week.

Laser therapy

- Use of a single laser type, the Q-switched ruby laser has been reported to be ineffective in 11 patients with melasma refractory to other types of therapy.
- Only two patients showed improvement of their lesions, 3 had no change, and darker hyperpigmentation occurred in 4 patients at 4 weeks.
- Histopathological examination of pigmented lesions immediately after laser application indicated that not all pigment-producing structures were affected by a single laser treatment.
- Better results have been shown with a combination of pulsed CO2 laser with Q-switched alexandrite laser.

- Principle behind the treatment was that the CO2 laser would destroy abnormal melanocytes and the alexandrite laser would remove any remaining pigment left in the dermis.
- Eight patients with dermal-type melasma were pretreated with a 14-day course of tretinoin 0.05%, HQ 4%, and hydrocortisone 1%, after which they were treated with one pass of the CO2 laser and then 4 patients with one pass of the Q-switched alexandrite laser and the other 4 with no treatment.
- At 24 weeks after laser therapy, results showed that the combination therapy was more effective in removing all hyperpigmentation areas.

Dermabrasion

- Kunachak, Leelaudomlipi, and Wongwaisayawan have reported a large-scale study on dermabrasion in 533 patients with facial melasma.
- Treatment involved local dermabrasion or full-faced dermabrasion with a 16-mm diameter coarse grit diamond fraise with the patient under local anesthesia; the skin was dermabraded down to the level of the upper or mid dermis.
- Of the 410 patients followed up for a mean of 5 years (range 1-9 years), 398 (97%) achieved persistent clearance of melasma.
- Partial recurrence occurred in the other 3% of cases.

- Complications were encountered in 3 cases (0.7%); two patients developed hypertrophic scars and one patient had permanent hypopigmentation.
- Pruritus was a common consequence in the early postoperative phase.
- Milia developed in most patients, although it was self-limiting

Consensus statement

- Therapies that can act at different stages of the melanogenesis process can produce better clinical results than a single compound acting at a single stage.
- First-line therapy for melasma should consist of effective topical therapies, mainly fixed triple combinations.
- Where patients have either sensitivity to the ingredients or a triple combination therapy is unavailable,other compounds with dual ingredients (HQ plus GA) or single agents (4% HQ, 0.1% RA, or 20% azelaic acid) may be considered as an alternative.

- In patients for whom therapy has failed, options for second-line therapy include peels either alone or in combination with topical therapy.
- Some patients will require therapy to maintain remission status and a combination of topical therapies should be considered.
- Lasers should rarely be used in the treatment of melasma and, if applied, skin type should be taken into account.

Level and quality of evidence for melasma therapies

Therapy	Level	Quality
Topical		
2% HQ	II-ii	C
4% HQ	I	B
0.1% tretinoin (RA)	I	B
0.05% RA	I	C
0.05% isotretinoin	II-ii	C
4% N-acetyl-4-S-cysteaminylphenol	III	C
5% HQ + 0.1%-0.4% RA + 7% lactic acid/10% ascorbic acid	III	C
3% HQ + 0.1% RA	III	C
4% HQ + 0.05% RA + 0.01% fluocinolone acetonide	I	A
2% HQ + 0.05% RA + 0.1% dexamethasone (modified Kligman)	III	C
2% HQ + 0.05% RA + 0.1% dexamethasone (modified Kligman) + 30%-40% GA peel	III	B
5% HQ, 0.1% RA, and 1% hydrocortisone	III	C
4% HQ + 5% GA	II-ii	B
4% KA + 5% GA	II-ii	B
2% KA + 2% HQ + 10% GA	II-iii	C
2% HQ + 10% GA	II-iii	C
4% HQ + 10% GA	I	B
20% Azelaic acid	I	B
20% Azelaic acid + 0.05% RA	III	C
Vitamin C iontophoresis	II-I	C
Adapalene	II-ii	B

Chemical peels		
10%-50% GA	I-ii/III	C
10% GA + 2% HQ + 20%-70% GA	II-ii	C
20%-30% GA + 4% HQ	II-i	B
70% GA	II-i	B
Jessner's solution	II-i	C
20%-30% salicylic acid	III	C
1%-5% RA	III	C
50% GA + 10% KA	III	C
Laser therapy (+chemical peels and topical therapies)		
Q-switched ruby	IV	C
Pulsed CO2 + Q-switched alexandrite	IV	C
Q-switched alexandrite	IV	C
Q-switched alexandrite laser + 15%-25% TCA peel + Jessner's solution	III	C
Erbium:YAG	III	D
Dermabrasion	II-iii	E

- Newer and upcoming therapies for melasma

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Newer and Experimental Agents

- **Aloesin-** derived from aloe vera and competitively inhibit hydroxylation of tyrosinase to DOPA and oxidation of DOPA to dopachrome.
- Choi *et al* studied the inhibitory effect of aloesin on human volunteers in a randomized comparative trial where the subjects were UV irradiated (210 mJ) on volar forearm and were divided into 4 groups: vehicle control, aloesin-treated, arbutin-treated and aloesin and arbutin-treated.
- The results revealed that aloesin suppressed pigmentation by 34%, arbutin by 43.5%, and the co-treatment by 63.3%, compared with the control ($N = 15$; $P < 0.05$) and in a dose-dependent manner.

- **Flavanoids:**
- They have the advantage of formulation into nanocapsules so that they are protected until they reach an active site of melanin synthesis where they exert a powerful reducing action, have antiradical activity, and act as a substrate competitor for the tyrosinases.
- An *in vitro* comparative study of this bioflavonoid factor on skin implants incubated for 15 hours with L-dopa and 0.1% bioflavanoids, control explants, and reference (1% hydroquinone) explants showed that bioflavonoids totally inhibit pigment induced by DOPA oxidation.
- Depigmentation action of bioflavonoids was supported histopathologically too.

- **Ellagic acid:** It's a naturally occurring polyphenol isolated from strawberries, green tea and geranium and acts by dose dependant inhibition of tyrosinase activity in B16 melanoma cells comparable to arbutin.
- In a study on guinea pigs, ellagic acid prevented UV-induced pigmentation similar to hydroquinone.
- In a study on guinea pigs, 6 weeks oral intake of ellagic acid was found to produce similar whitening effect as L ascorbic acid.
- Skin-whitening effect of ellagic acid is probably due to inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in melanocytes, without injuring cells.

- **Gentisic acid:** It is derived from Gentian roots and is a safe and effective topical skin lightening agent.
- Its alkyl ester, especially methyl gentisate is highly effective and less cytotoxic than hydroquinone.
- In a comparative *in vitro* study by Curto *et al*, 4 depigmenting agents, namely hydroquinone, kojic acid, arbutin, magnesium ascorbyl phosphate and synthetic esters of gentisic acid were studied for their tyrosinase inhibitory effects where mammalian melanocyte cell cultures and cell-free extracts were used.
- Study demonstrated that the smaller esters of gentisic acid shared an ability to inhibit melanogenesis without cytotoxicity and mutagenesis.

- **Hydroxycoumarins:** Coumarins are lactones of phenyl propanoic acid with benzopyranone nucleus.
- Natural derivatives of coumarins include aloesin, which has been proven to have tyrosinase inhibitory properties.
- Hydroxycoumarins are novel antioxidants, which have alpha tocopherol like structure and strongly inhibit tyrosinase in cultured human melanocytes and cell homogenates, besides having scavenging and quenching activities.

- **Natural derived botanical extracts:** A recent trend is to develop newer natural derived extracts for the purpose of skin lightening.
- In an *in vitro* study by Hwang *et al*, 101 plant extracts were studied for inhibitory effect against tyrosinase, L-dopa oxidation and melanin synthesis in B16 melanoma cells.
- Of these extracts, *Broussonetia kazwoki*, *B. papyrifera*, *Cornus officinalis*, *Rhus javanica* and *Pinus densiflora* inhibited tyrosinase and DOPA oxidation in dose-dependent manner.
- These botanicals have the advantage of being efficacious, and most importantly, they would be the drugs of choice in future being free from any complications.

- **Rucinol (4-n butyl resorcinol):** It is a phenolic derivative, which inhibits both tyrosinase and tyrosinase related protein.
- In a prospective, double-blind, randomized, vehicle-controlled, split-face comparative trial, 32 female patients with melasma were treated with rucinol serum 0.3% or vehicle, which was applied twice daily for 12 weeks followed by a 12 week follow-up.
- After 12 weeks, clinical pigmentation scores were lower than the vehicle-treated site, and the difference was statistically significant ($P < 0.027$).
- This preliminary study demonstrated the tolerability and efficacy of rucinol in melasma.

- A recent modification of 0.3% serum into 0.1% liposomal cream, which leads to an improved stabilization and enhanced penetration, has been studied to be effective in melasma.
- In a study by Huh *et al*, 23 patients with melasma were included in a randomized, double-blind, vehicle-controlled, split-face study with rucinol cream compared to vehicle-applied twice daily for 8 weeks, and significant (*P* value 0.043) improvement was seen in melanin index with more than 60% patients reporting subjective improvement.

- **Soy:** It is a plant derivative found in tofu products as well as in soyabeans and soy milk.
- Its primary metabolites genistein and diadzein have the active ingredients STI (Soy Trypsin Inhibitor) and Bowman Birk Inhibitor (BBI), which act by inhibiting melanosome transfer to keratinocytes and also have antioxidant properties.
- Wall *et al* conducted a parallel, randomized, double-blind, vehicle-controlled study with 65 female patients with mottled pigmentation where the preparation was applied twice daily for 12 weeks.
- There was a significant improvement ($P < 0.005$) in pigmentation, skin tone and texture in the treated group.

- **Silymarin:** It's a naturally occurring polyphenol flavanoid compound or flavolignans, derived from thistle plant Silybium marinum, which has been found to have inhibitory effects on melanogenesis in mouse melanocyte cell lines.
- However, the human studies for role in melasma are lacking.

- Alphalipoic acid / thioctic acid / dihydrolipoic acid: It's a disulphide derivative of octanoic acid and is known as a universal antioxidant for it is both fat and water-soluble, and thus acts in both lipid cell membrane and aqueous compartment of melanocytes.
- The newer combination product with zinc that is sodium zinc dihydrolipoyl histidinate has been studied by Tsuji Naito *et al* on B16 melanoma cells and found to inhibit dopachrome formation.
- It may thus act as a novel skin lightening agent for melasma, provided human trials are undertaken.

- **Dioic acid**: It belongs to the dicarboxylic acid group, which have 2 carboxylic acid with carbon atoms ranging from 2 to 24.
- A study by Tirado-Sanchez *et al* on 96 Mexican female patients with melasma showed that dioic acid is an effective and highly tolerated skin product for melasma.
- It was an open, comparative, 12 week trial in which MASI scores were compared between patients applying dioic acid twice and 2% hydroquinone cream twice daily.
- Although the difference in efficacy or side effects was not found to be significant (*P* value 0.287) between the 2 groups, the pre and post-treatment (after 12 weeks) difference in MASI scoring was significant (*P* value 0.001).

- **Green tea:** This most popular beverage has green tea phenols (epigallocatechin, catechin, gallocatechin gallate and epicatechin gallate) of which, the most important and pharmacologically most potent is epigallocatechin gallate (EGCG), which has been demonstrated to modulate melanin production in dose-dependent manner and also posses antiinflammatory properties.
- Dong *et al*studied the mechanism of action of EGCG on Mel Ab cells *in vitro* and found that it downregulates MITF and tyrosinase production.
- However, the studies of green tea phenols in human beings are limited because of stability and penetration issues.

- **Octadecenedioic acid:** is a dicarboxylic acid with structural similarity to azelaic acid.
- ODAs have been studied *in vivo* in a clinical comparative study on 21 Chinese volunteers where 1% ODA cream was applied on forearm for 8 weeks with a further follow-up of 4 weeks and compared to an application of 2% arbutin applied on the other forearm.
- The assessment was done by chromometric and mexametric analysis at baseline and every 2 weeks for 12 weeks where the melanin index decreased by 21.2% in 76% volunteers, and there was lightening effect in 90% individuals by upto 11%.
- Its main advantages are its flexibility in formulations over a broad pH range

- **Orchid extracts:** Tadokoro *et al* conducted a double-blind, comparative, split-face, prospective trial on 48 female patients with melasma and/ or lentigines to assess an *in vivo* efficacy of a cosmetic formulation containing orchid extracts, compared to 3% vitamin C derivative.
- The patients applied the orchid extracts cream formulation and 3% vitamin C formulation on either side of the face for 8 weeks, and the efficacy was evaluated clinically by colorimetric measurements and subjectively using a questionnaire, which showed improvement with both modalities.
- Thus, the study highlighted that the orchid-rich plant extracts possess efficacy, similar to vitamin C derivative in whitening melasma and lentigines.

- Mequinol / 4 hydroxy anisole: It is a derivative of hydroquinone, which is a more effective competitor of tyrosinase and has lesser side effects.
- In a pilot, small case series of 5 men with melasma by Keeling *et al*, the topical solution of 2% mequinol and 0.01% tretinoin was applied twice daily for 12 weeks and patients followed for 16 weeks.
- Complete clearance was noted in 4 patients, and moderate improvement was noted in single patient, and the results were maintained at follow-up 4 weeks after discontinuation of drug.
- The drug was well-tolerated however, the study size was small.

- **Linoleic acid:** unsaturated fatty acid, derived from safflower
- Accelerate tyrosinase degradation and accelerates turnover of stratum corneum.
- Lincomycin inhibits melanogenesis post-transcriptionally.
- In a study by Lee *et al*, it was observed that 2% lincomycin mixed with 0.05% betamethasone valerate and 2% linoleic acid caused significant improvement in pigmentation ($P < 0.05$) in 47 patients with melasma in a 6 week, double-blind, randomized-controlled trial as compared to vehicle or lincomycin with betamethasone, with the formulations to be applied every night for 6 weeks.
- Newer liposomal formulation of linoleic acid (0.1%) enhanced efficacy at lower concentration possibly by enhanced penetration of linoleic acid into melanocytes.

- **Magnolignan:** It is a phenolic derivative, which decreases maturation of tyrosinase and accelerates its degradation
- Its cream formulation (0.5%) was studied by Takeda *et al* on 51 female patients with melasma in an open study for 6 months, which showed significant subjective improvement and improvement in MASI scores in pigmented areas (*P* value < 0.05) without any side effects.
- A double-blind, randomized, comparative, clinical trial was conducted on 43 subjects to assess the effect of magnolignan on UV- induced pigmentation, which showed significant decrease in the pigmentation scores after 3 weeks of application of 0.5% magnolignan cream versus placebo and no serious side effects.

- **Tranexamic acid:** have antiplasmin activity and hence decreases alpha-MSH, which stimulates melanin synthesis.
- In an open study by Lee *et al* on 100 Korean women with melasma, tranexamic acid given intradermally (4 mg/ml) every week for 12 weeks caused significant decrease in MASI score (*P* value < 0.05), and 76.5% subjects reported lightening of melasma.
- It is temperature-stable, not UV sensitive and does not get oxidized easily,{ideal choice for skin lightening creams}.
- Fox did a clinical trial on 25 melasma patients in which tranexamic acid emulsion was applied for 5 to 18 weeks, and 80% subjects reported marked subjective improvement within 8 weeks without any significant side effects.

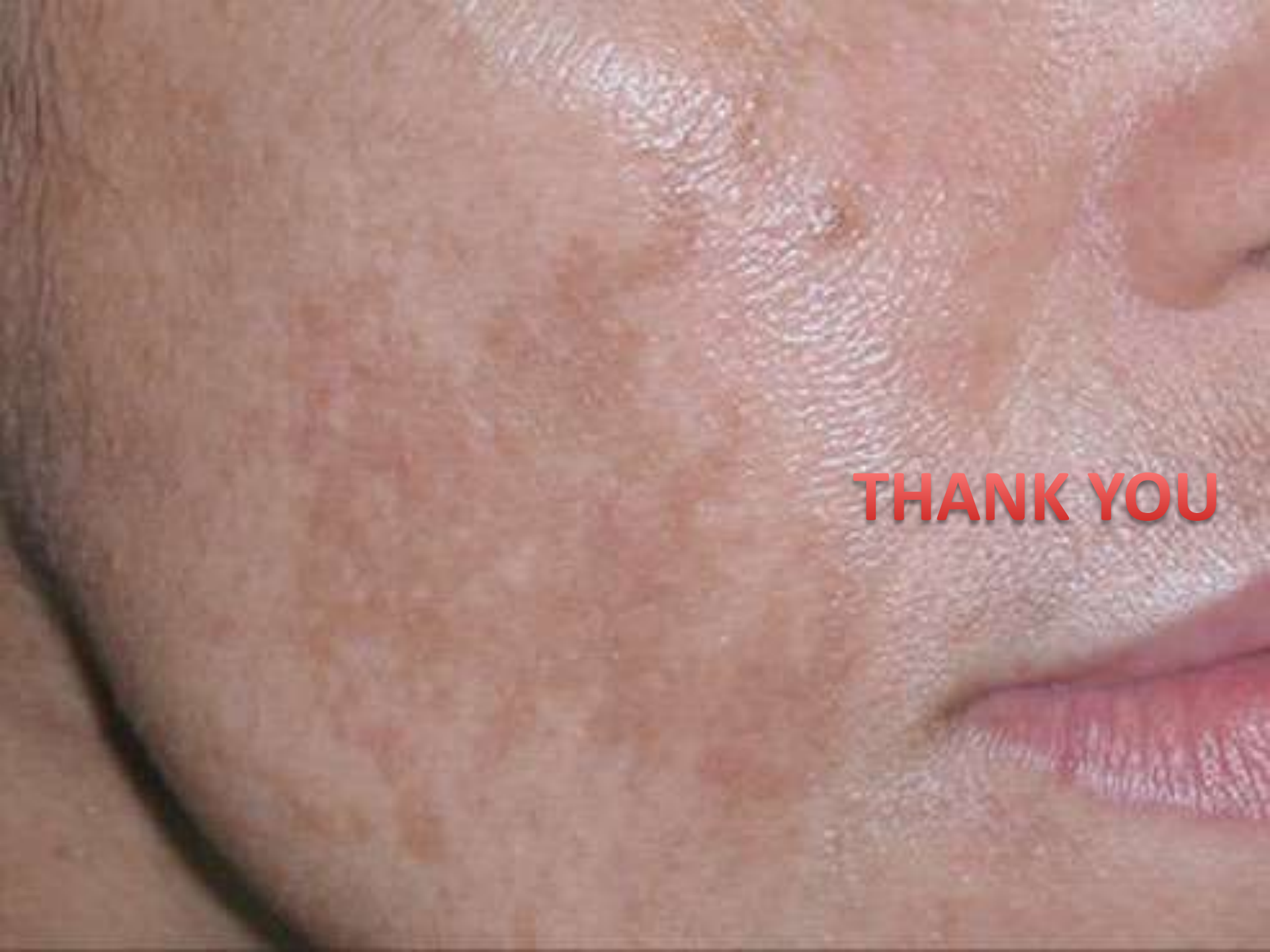
- **Cinnamic acid:** phenylpropanoid derivative, occurring in plants of cassia and ginseng, which inhibits tyrosinase activity as studied on human and guinea pig melanocytes.
- In an *in vitro* study on human and guinea pig melanocytes (Melan A), treatment with 100 ppm of cinnamic acid resulted in significant reduction in melanin production
- In a study by Tan *et al*, cinnamic acid (2 mmol/L; 0.5 mmol/L) showed tyrosinase inhibitory activity, which was significantly higher than hydroquinone (0.5 mmol/L)

- A novel formulation **pyronyl acrylic acid esters**, which shares the structural features of kojic acid and hydroxylated cinnamic acid, was studied in an *in vitro* study by Kang *et al* for its inhibitory action on tyrosinase enzyme and was found to be more efficacious than kojic acid.
- **Pidobenzone /k5 lipogel:**
- In a prospective trial by Zanieri *et al.* on melasma patients, topical treatment with pidobenzone 4% applied twice daily for 16 weeks caused reduction in MASI scores by at least 50% in as many as 70% patients.
- It may serve as a useful, reliable and safe treatment for this relapsing resistant condition

Agents Acting At Molecular And DNA Levels

- Antisense oligonucleotides (ASOs), which modulate the synthesis of tyrosinase, TRP1 and TRP2 by interacting with targeted mRNA at translational level, have also been investigated for their *in vivo* and *in vitro* depigmenting effects.
- A RCT was conducted on 30 Asian women with pigmented spots, and the formulation was applied twice daily for 8 weeks on pigmented and non-pigmented skin, which showed the lightening effect produced by the formulation to be significant ($P < 0.05$) in both the pigmented and non-pigmented skin as assessed by objective parameters.
- Thus, these antisense nucleotides are a new generation of active cosmetic ingredients with safety and stability, which can be utilized in melasma.

Mechanism of action	Plant derivatives	Non-plant derivatives
Competitive tyrosinase inhibition	Azelaic acid, arbutin, deoxy arbutin, aloesin, kojic acid, flavanoids, saponin, oregonin, yohimbine	Hydroquinone and its derivatives e.g. mequinol, N-acetyl-4-S-cysteaminylphenol and gentisic acid; glutathione and epicatechin
Non competitive tyrosinase inhibition	Glabiridin, hydroxystilbenes (Resveratol, Genitol); piceatannol; mulberry; polyphenols	Haginin A and N Acetyl Glucosamine
Newer tyrosinase inhibitors(require further *in vivo* and *in vitro* studies)	Diaryl propane	Hydroxyphenol naphthol; calycosin and quinolines
Reduces the transfer of melanosomes from melanocytes to keratinocytes or melanin transfer (serine protease inhibitors)	Niacinamide; soy (Soyabean trypsin inhibitors)	
Reduces tyrosine oxidation	P coumaric acid	
Copper chelation, antioxidant and inhibits melanocyte proliferation	Ascorbic acid; ellagic acid	
Removes keratinocytes, shortens cell cycle, and facilitates rapid pigment loss, interferes with pigment transfer and penetrates penetration of other agents	Liquirtin	Hydroxyl acids; retinoids


THANK YOU