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Integration of technology is current need of melasma regimen: A review

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ABSTRACT

Melasma is the most common skin disorder and natural defense mechanism of skin. Many factors exogenous and endogenous stimulate the melanogenesis and most common cause is found to be ultraviolet radiations, pollution apart from hormone imbalance.The complicated skin disorder is intractable & reappears. Newer medical devices, the exfoliating agents glycolic acid and other AHA's, chemical peels like trichloroacetic acid (TCA), retinol, salicylic acid, phytic acid and combination peels have been used to treat the refractory melasma. Natural compounds with skin bleaching molecular structure like resorcinol, resveratrol, aloesin, lignin peroxidase and many more are commonly added to skin formulations. Efficacy and safety of some of these natural active ingredients have been studied with clinical trials. Pigmented and vascular lasers are under study to be used as an adjunct therapy to topical treatments. Newer clinical objective assessment devices, like colorimeter & diagnostic devices like dermoscope, a non invasive dermal imaging of skin by diffused reflectance spectrometry to assess the in vivo damage and efficacy of therapy have been added. These tools assist in designing the effective treatment protocol of the therapy and any modification required during the treatment. To date doctors and scientists are trying to achieve the satisfactory lightening, delay recurrences or complete relief from melasma, but pathogenesis of melasma is very complicated and still under research. Hence synergy of technology can help doctors to a large extent in alleviating the problem and satisfy the patient's curiosity. Accordingly scientists and doctors are exploring integration of different available modalities with different modes of actions to inhibit melanogenesis and angiogenesis simultaneously.

***Key Words**: Melasma, Alpha-hydroxy acid peels, Depigmenting agents, Vascular laser, Pigment Lasers, Molecular therapy*

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INTRODUCTION

Hyperpigmentation is bilateral damage to the skin of the face repeatedly exposed to UV radiations. Excessive exposure to sun rays splits the DNA.It is acquired symmetrical disarrangement of melanosomes in melanocytes. Skin is preserved through melanin pigment, a chromophore to protect the skin from damage by UV radiations. These radiations are absorbed by melanin which then generates free radicals and photons before they damage other cell organelles. Excessive exposure to sun rays splits the DNA and melanogenesis is initiated by fragments of damaged DNA, thymidine dinucleotide (pTpT) which prompts the melanocyte to produce melanosomes which are transferred to keratinocytes through paracrine activity of the skin. It is proliferative and becomes chronic if not treated in time for a longer period. Hyperpigmentation is further evaluated based on objective and subjective evaluation tools into melasma, post inflammatory hyperpigmentation (PIH) and photodamage. It is refractory in nature and recurrence is very common. Excess exposure to UV radiation can lead to skin cancer. [1]

Quality of Life and Melasma

Multiple studies conducted over the last 20 years explored on quality of life of people having severe melasma lesions. Patients undergo considerable physiological and psychosocial distress. [2] Patient's quality of life is important to be assessed before the start of treatment to plan an effective treatment with counseling of management of disorder. Patients are very anxious to get relief from the problem. [2]The factors identified to correlate MASI and MELASQoL scores did not exhibit any interdependence. It does cause emotional distress and has a negative impact on patient's social life. Occurrence of hyperpigmentation on face upsets patients of all age groups, economic strata and of any level of education. [3]

Pathogenesis

Melanogenesis is an intricate process. There are many biochemical pathways and signals involved in its regulation which are disturbed due to many factors like UV radiations, hormone imbalance, pollution or

systemic diseases. Major origin of pathogenesis is considered to be UV radiation. [4]Sometimes changes are independent of UV radiations (Table 1).

Hyperpigmentation of face is also known as melasma, photodamage & post inflammatory hyperpigmentation. Stress & bad lifestyle also stimulate melasma. Skin can be lightened with integration of new technologies including new lightening products with clinical trials, peels, Q switched laser, vascular laser ,radio frequency (RF) micro-needling can assist in giving better outcome of a therapy. The melasma patients should undergo objective and subjective evaluation before therapy, during the therapy and post therapy. Colorimeter and dermoscope devices are good tools to assess the improvement and guide doctors accordingly. Some required biochemical parameters need to be tested. This diagnosis can assist doctors in customization of the treatment for an effective outcome to the satisfaction of patients.

Topical Approach

Topical steroids and hydroquinone (HQ) is the most preferable and first line of treatment. HQ cream is considered the gold standard even today in spite of many disadvantages and also due to lack of studies on new ingredients. Kligman's formula triple combination cream containing HQ is used very commonly. Deleterious effects like contact dermatitis, exfoliation of skin, increased sensitivity and stinging sensations are induced if used for more than 8 weeks. Serious problems which are not so frequent unless used for long time without professional guidance can occur like leukoderma, hypochromia, and ochronosis. Therefore, there is need to develop more topical products which are safe and clinically proven.

Peels like glycolic acid (GA), trichloroacetic acid (TCA), Jessner's solution and pyruvic acid have already been studied on melasma patients. It is also observed that desirable results cannot be achieved with monotherapy like peels or topical formulations or laser therapy alone. Glycolic acid (GA) is an alpha hydroxy acid. They are hydrophilic by nature. They are mild to moderate peels. The AHAs are used in skin problems related to hyper-keratinization. The AHAs enhance the process of exfoliation by reducing the cohesion between corneocytes hence can help in penetration of therapeutic creams faster for better results. These peels along with the lightening agents can help in alleviating the epidermal, dermal and mixed hyperpigmentation; and UV induced photodamage. Glycolic acid is the best exfoliating peel in the family of alpha hydroxy acid peels, as its molecule weight is lower than other AHAs. It is extracted from sugarcane juice. Family of AHAs includes citric acid (orange /citrus), mandelic acid (almond), lactic acid (milk), malic acid (apple), tartaric Acid (TA) and pyruvic Acid (PA). It is important to know the basic factors concerning its efficacy and safety before use like pH, concentration, endpoint & bioavailability (available free acid concentration). Results on hyperpigmentation depend on above factors and method of application. Safety factors like application time of glycolic acid, endpoint, neutralization and side effects like burning can occur hence post inflammatory hyperpigmentation or more serious dermal pigmentation which is difficult to treat. [25] A study was done on the efficacy of 40% glycolic peels in melasma in 50 patients. Patients were in the age group of 21 to 45 years. They were divided into 3 groups. All the patients were given a set of 6 peelings at an interval of 15 days. Out of 50 patients, one (2%) patient achieved 75% improvement, 7 (14%) patients had achieved 51- 75% improvement, 20 (40%) patients achieved 25-50% and 16 (32%) had less than 25% improvement. Two patients developed post inflammatory hyperpigmentation. More than half experienced erythema and complained of stinging sensation. Hence it was concluded that peel alone cannot give total clearance but it can improve skin quality. [26]Azelaic acid (AzA) is derived from the yeast or fungus *Pityrosporumovale*. It is also known as nonanedioic acid. It is anti-inflammatory, antimicrobial and comedolytic. Therefore it helps in clearing acne vulgaris, rosacea and hyperpigmentation. It has a 9 carbon chain with two carboxylic acids attached to it. It inhibits inflammatory mediators which are sometimes primary cause of stimulation of melanogenesis. It competitively inhibits tyrosinase, deoxyribonucleic acid (DNA) synthesis and mitochondrial oxidoreductase. It acts as an antioxidant. An open label trial was done on 29 melasma patients with 20% azelaic acid and compared with 4% hydroquinone cream. Assessment of lightening was done subjectively with Melasma Area Severity Index (MASI) score. The authors concluded that reduction in melasma pigmentation was better with azelaic acid as compared to the hydroquinone group after 8 weeks**. [27**] Further trial of 15% azelaic acid gel was conducted on 20 patients having skin type IV to VI. Gel was applied twice daily for time span of 16 weeks. Outcome of the treatment was significant relief in acne and post-inflammatory hyperpigmentation (PIH). Investigator's global assessment (IGA) score demonstrated reduction. [28]Another controlled trial was done in India with 20% AzA cream on 60 patients. Comparative study was done on two groups with 30 patients each having epidermal melasma. One group was treated with a glycolic acid peel once in 21 days and 20% AzA cream application two times a day to the entire face. Second group was treated with only AzA cream. A significant reduction was seen in AzA with glycolic acid group as compared to only AzA control group.[29] A comparative split face study was conducted on the efficacy of 50% glycolic acid against the combination of azelaic acid 20%,

resorcinol 10%, phytoceuticals acid 6% (Triple combination). All the 42 patients were treated with triple combination peeling on the right half face. Contralateral face was treated with 50% GA peel. Time interval between two peel procedures was 15 days. Erythema was the endpoint for glycolic acid 50% peel but even if it was not achieved, face was washed in 5 minutes. Triple combination was applied on face for 10 minutes and washed after the fixed time. Therapy was completed with set of 6 sittings. There was minimal difference in outcome between 50% glycolic peel as compared to triple combination on MASI score.[30]Trichloroacetic acid (TCA), is a chemical peel having proteolytic properties and lactic acid is an AHA which removes the cohesion between corneocytesand exfoliates the skin. When combined with TCA it initiates inhibition of melanosynthesis. It was found that combination peel inhibits the activity of those enzymes that are responsible for degradation of collagen and elastin, and the production of melanin pigment. The combination of two different peels gave better output than single peel due to different mechanism of action. Sequential docking using Rosetta software explained the phenomena that possibly TCA transform its linear structure to the ring-like structure. In-vitro results on collagen and elastin were confirmed by up-regulation of COL 1A, COL 3A, fibronectin, and elastin gene expression from treated 3D human skin with the combination peel. The ex-vivo testing on human skin, irradiated with dose of 6 J/cm2 confirmed the results on biopsy. Combination peel significantly inhibits melanogenesis and improves photo-damage. [31]

Retinoic Acid

Retinoic Acid (RA) or tretinoin has proven efficacy on photoaged skin. The results of RA peeling can be appreciated after few months curatively and satisfy the patients. One study on tretinoin peeling was done to demonstrate the visual and structural changes of the skin after five treatment sessions. Fifteen female patients were included in the study. The tretinoin peel concentration of 1-5% was applied twice a week to all the patients. Punch biopsy was conducted to see before and after changes in histology. The skin texture and appearance were noticed clinically. Histological improvement exhibited increase in the thickness of epidermal layer and decreased in corneous layer. Hence number of tretinoin peelings demonstrated good histological results and clinically also improved photo-aged skin grade I and II, melasma, ephelis, and acne grade I. It was also quicker and without any side effects. [32] Additionally topical tretinoin was also studied for other pigmented lesions, for example liver spots and melasma on thirty-eight women in a vehicle-controlled study. Patients were randomly divided into two groups of 19 numbers each. 0.1% tretinoin was applied to the face of one group and the entire face of patients of second group weretreated with vehicle cream once daily for 40 weeks. Clinical improvement was seen in 13 (68.40 %) of 19 tretinoin-treated patients compared to just one (5.26 %) of 19 in the vehicle group (P 0.0006) after 24 weeks. Statistical improvement in MI and EI with colorimetry was appreciable exhibiting a 0.9 unit lightening of tretinoin-treated melasma and a 0.3 unit darkening with vehicle (P = 0.01). Histological studies showed 36% reduction in epidermal pigmentas compared to50% increase with vehicle (P 0.002).Visible exfoliation and erythema were observed in 88% of tretinoin-treated and 29% of vehicle-treated patients. Hence considerable improvement in melasma was noticed with topical 0.1% tretinoin due to reduction in epidermal pigment but process was very slow.[33] Further, a randomized, vehicle-controlled trial on the efficacy of topical 0.1% all-trans-retinoic acid (tretinoin) was done in the treatment of melasma in 30 black patients (American -African). Twentyeight of the 30 black patients with melasma completed a 10-month clinical trial. The patients were selected randomly and divided into two groups. One group prescribed 0.1% tretinoin and other groupwas to apply vehicle cream daily to full face for 40 weeks. The MASI score showed 32% (4.48) improvement in the group applying tretinoin compared to vehicle cream treatment group exhibiting 10% (1.5) improvement. Lightening of melasma correlated well with the MI measurement of colorimetry after 40 weeks of tretinoin treatment as compared to vehicle group. Histological study of skin lesion showed appreciable decline in epidermal pigmentation in the group applying tretinoin group against vehicle group. Mild "retinoid dermatitis" was noticed in 67% of tretinoin-treated patients. Therefore it was concluded that 0.1 % tretinoin can effectively reduce melasma in black patients with no complications. [34]

Topical tranexamic acid (TXA)

It is a known haemostatic agent synthetically derived from lysin. TXA is inhibitor of fibrinolysis. Its mode of action is blocking reversibly the lysine binding sites on the plasminogen proteins. Off label it is also used to suppress melasma. One school of thought is that it may be blocking the keratinocyte- melanocyte interaction reversibly. It also normalizes the excess vascularisation**.** It is used in different forms in melasma from oral prescription,to topical cream or mesotherapy (microinjections at site). Efficacy needs to be proven by more clinical trials. [35] TXA trial for the treatment of melasma was conducted to see its efficacy on 23 patients having melasma. Topical formulation with 2% TXA was applied to the face for 12 weeks. Evaluation techniques used were mMASI score and objective evaluation was done with chromameter. Histological changes were studied in ten patients through skin biopsies for pigmentation

and vascularity. Expressions of paracrine factors (FGF, Wnt& TGF-B) were also assessed as they play major role in melanin synthesis. Considerable reduction was observed in melanin content of the epidermis. The ET-1, VEGF expression was down regulated along with decrease in CD31-positive vessels number. Hence, it was concluded that topical TXA is effective for melasma. The suppression of ET-1 could be one of the modes of action of TXA on reduction in hyperpigmentation. [37] Further a new study was done in a span of 12 weeks on Brazilian women with skin type 1-IV. The clinical trials were conducted with a new formulation with composition 3% TXA, 1% kojic acid, and 5% niacinamide to see the efficacy on melasma and PIH. Efficacy evaluations were performed at baseline 0 week and weeks 2, 4, 8, and 12, using subjective and objective measurement tools along withpatient'sselfassessment questionnaire. A measurable improvement was observed from week 2 and continued. There was significant reduction by week 12 without any side effect. The theory was put forward that TXA control pigmentation by down-regulating the co-activators causing inflammation which initiate melanogenesis. In vitro data explores that TXA act by mediating the inhibition of stimulation of human melanocytes by prostaglandin-2. [37]A new topical formulation of TXA in combination with niacinamide was developed to study its efficacy on pigmented patches of skin. Forty two Korean women subjects, having intractable pigmentation such as melasma and post-inflammatory hyperpigmentation (PIH) were included. Experimental group of 21 subjects were prescribed depigmenting cream formulated with 2% niacinamide plus 2% TXA to be applied twice daily and control group of 21 women applied moisturizing cream in addition to sunscreen each morning. Pigmentation was measured with skin calorimeter. The depigmenting formulation containing niacinamide + TXA active ingredients in combination was significantly more effective than the placebo formulation of moisturizing cream in reducing the appearance of pigmentation and reduction in facial hyperpigmentation. [38]

4-n-butyl resorcinol (Rucinol) (4nBR)

Rucinol is another name for 4-n-butyl resorcinol. It is apotential compound having the property of bleaching the hyperpigmented skin**.** The concept of 4-n butyl resorcinol bleaching in melasma has been known since many years because of its strong inhibition ability of human tyrosinase.[44] Many natural compounds, mainly flavonoidsknown to be used as whitening agents and anti-inflammatory in nature contain the resorcinol as one of the ingredient. The Artocarpus plant extract in vitro showed tyrosinase inhibitory activity because of 4-substituted resorcinol design in its compounds such as artocarpanone, norartocarpetin, artocarpesin, artogomezianol, andalasin, artocarbene and chlorophorin.[41] Phenol-ethyl resorcinol action as anti-melanogenesis is due to activation of p44/42 MAPK, indicating it as potential therapeutic agent for treating melasma [42] Among the family of resorcinol derivatives, 4-butylresorcinol is a strongest tyrosinase and TRP-1 inhibitor. The availability of flavonoids is generally very low, so smaller resorcinol with high effectiveness and good availability was explored. The skin pigmentation reduction by well-known compounds with skin-whitening properties like hydroquinone, arbutin, kojic acid and 4-n-butylresorcinol were compared. The biochemical assay was used to assess inhibitory activity of human tyrosinase enzymeandthe cultured MelanoDerm™ skin model was used to study inhibition of melanin production.The immortalized mouse melanocyte cell line was used to explore the decolorizing activity of 4-n-butylresorcinol. Rucinol considerably suppressed the activity of melanin synthesis as per the different concentrations used. It was also seen that the activity of tyrosinase was suppressed. In vitro tool used demonstrated that 4-n-butylresorcinol considerably suppresses the activity of tyrosinase.It is also reported that 4nBR does not activate ERK (extracellular signal-regulated kinase) or Akt (AKT/PKB), a phosphoinositide-dependent serine/threonine protein kinase) which suppress melanin synthesis by down-regulating MITF (microphthalmia-associated transcription factor). Accordinglyit does not affect cAMP response element binding protein (CREB) phosphorylation which stimulates expression of MITF. It was observed if rucinol is added to hinokitiola natural monoterpenoid down-regulates the expression of MITF. Hence combination can inhibit melanin synthesis with synergyof two mechanisms of action. Thereforehypo melanogenesis by 4-n-butylresorcinol results from its direct inhibition of tyrosinase. [43] The clinical trials confirmed the in-vivo efficacy of 4nBR. The subjects having age spots on the forearms were selected for research. The formulation containing rucinol was applied twice daily on two age spots of the forearm of the subjects against two control age spots with the corresponding vehicle. Time interval of application was 8 weeks. The treatment with 4nBRlightened the age spots considerably, while vehicle treated control spots were visible as before. The ability of rucinol to suppress human tyrosinase outdo that of hydroquinone, arbutin and kojic acid is proven by present in vitro and in vivo data (Table 2). Hyperpigmentations reveals 4nBR as a very valuable active compound for the management of pigmentation disorders. [43] Efficacy of 0.1% resorcinol was explored on twenty women melasma patients of Korean origin, ten (50%), 6 (30%) and 4 (20%) patients of type III, IV and V respectively. All the patients completed the trial. After 4 weeks of application, a statistically significant

reduction in the mean melanin index (MI) was seen with 4-n-buylresorcinol. [44] An open label study of 0.3% 4-n-buylresorcinol was carried in 52 female subjects of melasma for its efficacy and safety. Skin was evaluated with MASI score and digital photography. There was significant decrease in pigmentation from baseline 14.73 to 6.48 at 8 weeks. Treatment was well toleratedhence it was found to be safe and effective. [45] Comparative study of 0.2% thiamidol**(**isobutylamido thiazolyl resorcinol) against 4% HQ was done on 50 women of phototypes III -IV having melasma to study & compare the efficacy and tolerability. 0.2% thiamidol applied twice a day in two layers in one group of 25 patients versus 4% HQ once at night in another group of 25 patients for 90 days. All the patients were given sunscreen. Diagnostics applied showed reduction in melasma hence the quality of life also improved. The GAIS analysis resulted in an improvement of 84% in the thiamidol group as against 74% in the HQ group. Only 8% experienced mild allergic contact dermatitis in the thiamidol group.[46] Another new proprietary formulation combining the phenyl-ethyl resorcinol, nonapeptide-1, aminoethyl phosphonic acid, antioxidants with sunscreen ingredient. This triple combination of actives was studied to compare against sunscreen alone in the management of melasma and its recurrence. The safety of the formulation & quality of life of the patients was also explored in this double-blinded parallel-group randomized study conducted on 46 subjects for 8 months. Patients were randomly divided into two groups of 23 each into control and active. The treatment was done in three stages. Stage 1, two selected groups applied proprietary formulation for eight weeks, in stage 2, one group applying proprietary medicine and the second control group applying sunscreen. In stage 3 all the patients were observed for the sustenance of results and relapse. Sunscreen was applied in all three stages. Group applying proprietary formulation in the study showed improvement in the melasma severity score. The proprietary formulation was having sunscreen as one of its constituents, is more effective in controlling relapse after the application of the active formulation. And avoid the inconvenience of applying two different formulations as compared to sunscreen alone**.**[47] Further a new formulation of combination of 4-n-butylresorcinol andresveratrol with two different mechanisms of action was studied on inhibition of melanogenesis. Aim was to achieve efficacy of combination without any side effects. It was found that combinations at low concentrations showed that concentration of 1 μM ofrucinol and 1 μM of RSV did not reduce hyperpigmentation independently as reported by Western Blot analysis but the combination of rucinol and RSV significantly reduced melanin synthesis. Increased concentration of 10 μM of 4-nBR and RSV (10 μM) reduced melanogenesis strongly. 4-nBR is reported to inhibit tyrosinase directly and resveratrol at a concentration of 0.1-10 μM with different modeof action reduced hyperpigmentation through post-transcriptional regulation of tyrosinase. When in combination they reduced tyrosinase levels. Hence results indicate that both function differently in reducing the activity of melanocytes with direct and indirect inhibition of melanosynthesis. The combined use of the two agents with different mechanisms of action can also have additive effects. Resveratrol with its multifunctional activity of suppressing melanogenesis when combined with other hypopigmenting agents may work in synergy**.**[48]Liposomal Encapsulated 0.1% 4nBR and RSV combination cream was evaluated for its efficacy and safety in the treatment of melasma. Twenty one female subjects with melasma were given topical cream to be to be applied to face every day for 4 weeks. Melanin index of the lesion was measured at week 0, 2 and 4, and periauricular skin with no lesion was measured with colorimeter. The MI of the lesion was measured at weeks 2 and 4. There was considerable reduction when compared to baseline while no change could be observed in the nonlesional skin. MI was observed throughout the study. The mean investigator's global assessment score was also significantly improved at weeks 2 and 4. Patients were asked to self-assess the change. 8 (38.1%) patients replied moderate improvement and 11 (52.3%) patients noticed considerable improvement with no or minimal side effects. Hence formulation was potent enough to show results in two weeks and also safe to be used.[49]Resorcinol alkyl glucosides 7-12 synthesizedfrom2,4-dibenzyloxybenzaldehyde is a novel tyrosinase inhibitors based on the structure of rhododendron. The tyrosinase inhibitory activity of 7-12 increased with the length of the alkyl spacer between resorcinol and glucose. The 50% inhibitory concentration (IC50) of tetradecyl derivative 12 was 0.39 μM, making it the most potent of the compounds synthesized. The IC50 of 8 (3.62 μM) with a propyl spacer was 10 times that of 7 (35.9 μM) with an ethyl spacer. This significant activity difference suggests that increase in alkyl spacer length when exceed C3, resorcinol alkyl glucoside and tyrosinase demonstrate better interaction.[50]

Cysteamine

Amino acid L-cysteine when degrades in human body, it produces cysteamine hydrochloride (ß–mercaptoethylanine hydrochloride). Cysteamine protect normal cells from radiations by suppressing free radical formation and induce natural antioxidants of the body. [51] Many studies were conducted on the efficacy of cysteamine in patients with melasma. In a randomized, double-blind trial of 50 patients, selected randomly for placebo and experimental treatment, 5% cysteamine was prescribed to be applied

one time at night. Assessment of efficacy was done with colorimetry, MASI score, Investigator's Global Assessment (IGA) and patients self assessment questionnaire. A significant improvement in melasma lesions was observed compared with patients who were treated with placebo. The cysteamine initiated significant reductions in MASI scores in a time span of 16 weeks compared with placebo. [52]

Herbal topicals which need more clinical trials

Gedunin (Neem)
Curcumin
Lignin peroxidase
Aloesin
Resveratrol
Oxy-resveratrol
Pine bark

Gedunin

Derived from Neem tree (*Azadirechta indica*), was studied for its anti melanogenesis property. Limonoid gedunin decreases α-MSH Production, inhibiting tyrosinase (TYR) activity and TRP1 protein amount without any toxicity. Zebra fish model experiment confirmed the results in vivo. All embryos treated at different concentrations did not show any growth abnormality but showed reduction in black spots and melanin content. The concentration applied was 100 μM which is highly active and much lower than kojic acid concentration of 8 mMused as control.Gedunin also showed inhibitory effect on melanogenesis in B16F10 mouse melanoma cell line. There was 20% reduction of tyrosinase activity with gedunin at a concentration of 50 μM compared to 12.4 % with kojic acid. Gedunin also decreased mRNA level of all the genes as per the concentration level of 25 and 50 μM in comparison to 200 μM dose of kojic acid as control. Levels of MITF and tyrosinase were also decreased by 0.10 and 0.26 fold at concentration of 50 μM, Thus gedunin proved to be more effective and this study demonstrated a new melanogenesis inhibitor and new ingredient for cosmetic formulation.[53]

Curcumin

A safer natural depigmenting active tetrahydrocurcumin was studied on 50 human subjects, a randomized, placebo controlled study demonstrated the comparable depigmenting effects of 0.25 percent tetrahydrocurcumin cream against 4 percent hydroquinone cream. This was a4 week trial. There were no side effects noticed from 0.25 % tetrahydrocurcumin cream but with 4% hydroquinone cream mild to moderate side effects were reported. Hence 0.25 % tetrahydrocurcumin cream can be considered as an effective and safe lightening ingredient in cosmetics instead of HQ.[54] The efficacy of curcumin from turmeric has been found in repairing the skin, depigmenting the skin patches and brightening the skin. The aim was to compare the efficacy of 0.25% turmeric extract cream against grated turmeric in lightening the skin. Twenty two women were selected randomly and split into two treatment groups. Group I applied 0.25% turmeric extract cream once a day in upper right arm and 4% HQ (control) in lower right and left arm. And group II applied curcumin cream twice on upper right arm and 4 % HQ (control) two times a day on lower right and left arm. Turmeric in grated form was applied only on upper left arm with the same protocol as curcumin cream in both the groups. The skin analyzer was used to measure the pigment intensity at day 0, 8, and 21. There was statistically measurable differences ($p<0.05$) observed between twice application of 0. 25% turmeric cream extract and 4% HQ at day 8 in lightening of the pigment.[55]

Lignin Peroxidase

The enzyme lignin peroxidase from fungus *Phanerochaetechrysosporium* acts by oxidizing and breaking down melanin. Lignin is having same structural formulae as melanin. Lignin peroxidase in rotting trees breakdown melanin resulting in decolonization. Fifty one Asian patients underwent a split face randomized, double-blind, controlled, paired, single-center study trial. Lignin peroxidase incorporated cream was applied on half side of the face against 2% HQ (placebo) applied on the contralateral face. Melanin index reduced rapidly on the experimental face side applied with lignin peroxidase cream. Marked lightening was observed on experimental face.[56]In another study mild-to-moderate reduction in facial hyperpigmentation in two groups of women was noticed after a span of 12 weeks. Group1 applied lignin peroxidase to experimental half face two times daily against placebo group where contralateral face was left without any treatment. Group 2 applied lignin peroxidase daily two times a day to one half of the face and 4% HQ at night to the other half. Evaluation was done with subjective and objective investigation with skin colorimeter at baseline, Weeks 2, 8, and 12. In Group 1, substantial reduction in skin lightening was observed on the face using lignin peroxidase cream against placebo group. In Group 2, lignin peroxidase cream showed significant difference as compared to HQ including

other parameters like skin texture, radiance, roughness, opacity and overall appearance. Hence lignin peroxidase can be a topical skin lightener which require more studies.[57]

Aloesin

Aloesin is a bio-active and chromone derivative isolated from the plant *Aloe vera*. It directly inhibits tyrosinase enzyme which play major role in melanogenesis. It also inhibits tyrosine 3-monooxygenase and L-3, 4-dihydroxyphenylalanine oxidase. Cell culture studies have shown that aloesin is direct inhibitor and reduction in melanin content is dependent on concentration of dose applied. The comparative study was done to see the inhibitory effect of aloesin and arbutin. Subjects were divided into 4 groups and their inner forearm was irradiated with 210 mJ. Each group was treated in a different manner with either control vehicle or aloesinoraloesin with arbutin and only arbutin. Aloesin and arbutin was topically applied four times a day for 15 days and results were compared. Aloesin reduced melanin content by 34%, arbutin by 43.5% and combination treatment by 63.3% when compared with controls. Hence it was concluded that aloesin may be used as an agent that inhibit tyrosinase enzyme. Pigment reduction was concentration dependent (n 7, $P < 0.05$). Therefore aloesin can be used as anti-inflammatory and depigmenting agent.[58] This new study has explored combination treatment of aloesin and arbutin in tyrosinase inhibition. The synergy of both active ingredients inhibits tyrosinase better than aloesin or arbutin separately by acting through a different mechanisms of action. Thereforeit is suggested to combine aloesin along with arbutin to inhibit melanin production by two different mechanisms of non-competitive and competitive inhibition of tyrosinase activity in synergy.Tyrosinase enzyme activity of both human enzyme and mushrooms was inhibited by aloesin with an IC 50 value of 0.1 mM and arbutin at an IC 50 value of 0.04 mM.Kinetics data showed that aloesin inhibit noncompetitively whereas arbutin did it competitively. Hence it is suggested to mixed together the aloesin along with arbutin inhibit melanogenesis by synergy of the mechanisms of inhibiting of tyrosinase. [59]

Resveratrol

Resveratrol is an active ingredient for cosmetology and dermatological applications. [60] It is also studied for its multifunctional topical depigmenting activity on human subjects. [61] Melanogenesis is provocated by cosmetics or sun burn on skin resulting in oxidative damage. Keratinocytes signals for more melanocyte hence creates hyperpigmentation. In the process of inflammation histamines are released triggering vasodilatation and increasing vascular permeability. Resveratrol controls the inflammatory processes and hence it stops signals of keratinocytes and protects them from oxidative damage which prevents the keratinocyte-induced melanocyte stimulation. Irregular hyperpigmentation is observed due to agitated basement membrane. Investigation resulted in proving that resveratrol restored the integrity of the basement membrane. Hence this study suggested that resveratrol indirectly regulates pigmentation by affecting keratinocytes. It is direct and indirect inhibitor of melanogenesis with various mechanisms of actions (Table 4).

Oxyresveratrol Natural

A naturally occurring analog. It is even more potent tyrosinse inhibitor than resveratrol with an IC50 value of 0.09 μM.[76] A concentration of only 1 μM of oxyresveratrol inhibits 50% of dopa oxidase activity. [77] It is a natural product found in *Melaleuca leucadendra and Soraceamuriculata*. It is a natural stillbenoid, unique skin lightening, anti aging and UV protection agent. The study on resveratrol, oxyresveratrol and acylated on a reconstituted skin model indicated that resveratrol derivatives can act as depigmenting agent modifying excess melanin synthesis and cell viability. It can be safely used in cosmetics with affectivity and stability inhibiting the tyrosinase activity. [77]*Cudraniacochinchinensis* stem extract contain potential active compounds having tyrosinase inhibitory properties. This indicates a great natural formulation can be developed. Its results showed that tyrosinase inhibitory activities of 2, 3-cis-dihydromorin (IC50 31.1 μM), 2, 3-trans-dihydromorin (IC50 21.1 μM), and oxyresveratrol (IC50 2.33 μM), were more potent than that of kojic acid (IC50 50.8 μM). [78]*Morus australis* stem extract containedoxyresveratrol a proven tyrosinase inhibitor. Unknown extracts of root and twig of same plant may have tyrosinase inhibitor properties which are not yet explored. Austraone A, together with 21 known compounds were isolated and explored for their anti melanogenic activity. Oxyresveratrol, moracenin D, sanggenon T and kuwanon O demonstrated stronger tyrosinase inhibitory activities than that of kojic acid and proved that *Morus australis* root extract compounds are potential tyrosinase inhibitors and can be a useful depigmenting ingredient in cosmetics and food formulations.[79]Resveratrol triacetate (RTA) is an analog of resveratrol having depigmenting property.Resveratrol at a concentration of 0.5 % initiates mild skin irritation but RTA is non-irritating at 0.4 %. RTA was evaluated for its depigmenting efficacy. The formulation containing 0.4 % RTA was evaluated in 22 patientswith two different test designs. In the artificial tanning design, the test product and the control product were applied twice daily to the skin of the forearms after pigmentation induction

by ultraviolet irradiation. Appreciable difference was noticed statistically (P< 0.05) in individual topology angle by 17.06 and 13.81 %, respectively. In the hyperpigmentation model, the test product and the control product were applied twice daily to the faces of 21 human subjects. There was a significant decrease in average intensity of the hyperpigmented spots from 2.67 % in the test group and 1.46 % in the control group. Therefore, RTA can be a choice in cosmetic formulation for depigmenting of human skin. [80]

MOLECULAR THERAPY

Inhibitory peptides

Peptides also help in down regulating the melanogenesis. They do not completely stop but they are competitive inhibitors. When badly damaged cells send messages for protection, peptide function is to stop the message till damaged cell dies or apoptosis happen.

EF-5 ECGYF

Tyrosinase down-regulators from natural sources are safe & have not been explored widely. Some proteins and peptides from milk, silk, sunflower and honey have potential to hinder the activity of tyrosinase and can be used as therapeutics for the hyperpigmentation problems of skin. EF-5, a new peptide with midasin protein, is recently investigated for its potential to hinder the activity of tyrosinase. It is also having antioxidant properties. EF-5 is a penta-peptide and stronger tyrosinase inhibitor than arbutin and glutathione.In-vitro studies exploredIC50 of arbutin, glutathione, and EF-5 were 5.73 mM, 1.18 mM, and 0.46 mM, respectively. EF-5 method of downregulating tyrosinase is not same as glutathione as witnessed by UV-Vis absorption and circular dichroism spectroscopies. EF-5 bind with tyrosinase by hydrogen bonds and hydrophobic interactions as predicted in molecular docking. EF-5 also retains scavenging activity with both hydroxyl and super oxide radicals in vitro and MIT assay proves its non toxicity. [81]

Oligopeptide (Lumixyl**)**

Lumixyl an oligopeptide is proprietary peptide which hinders the activity of tyrosinase in both mushroom and human. The split face, placebo controlled study was conducted, to explore the effect of 0.01% topical oligopeptide on moderate intractable melasma. It was a double blinded study and completed in over a 16-week. A group of five femaleswith photo-type IV were selected randomly with moderate recalcitrant melasma. Improvement was assessed with ten-point and five-point grading scales. Statistically significant improvement was noticed in lightening of melasma. Hence oligopeptide may be incorporated in the treatment of melasma [82]

D-tyrosine

The addition of an amino acid D-tyrosine an enantiomer of L-tyrosine to the terminus of short cosmetic peptides like anti-wrinkle Pentapeptide18, an antiaging tetrapeptide peptide 21 (GEKG) or an anti-inflammatory copper peptide (GHK-Cu) adds an antimelanogenic effect without modifying the actual cosmetic property.The reduction of melanin content was dependant on the concentration of D-tyrosinase in human MNT-1 melanoma cells and primary human melanocytes. 500 μM of D-tyrosine completely inhibited 10 μM L-tyrosine-induced melanogenesis. Provenwith L-DOPA staining MNT-1 and in vitro assays.Thus, D-tyrosine appears to be a competitive inhibitor of tyrosinase. It also downregulates the synthesis of melanin prompted by two other factors,Alpha MSH and UV radiation. It is confirmed that D-tyrosine reduced melanin synthesis in the epidermal basal layer of a 3D human skin model. The research data confirms its depigmenting activity by directly down regulating tyrosinase activity.[83]

MITF-siRNA (Microphthalmia associated transcription factor-small interfering ribonucleic acid)

MITF-siRNA cream for depigmenting was developed with an addition of trans-dermal peptide which expedites the penetration of MITF-siRNA in epidermis and dermis of mouse skin effectively and downregulates the expression of MITF. This significantly hinders the activity of tyrosinase and reduces TRP1 and MC1R hence reduction in melanogenesis. A 12 week study was conducted with the new formulation and reduced the melasma significantly (P<0.001).The clinical evaluation demonstrated 90.4% lightening. MI from colorimeter showed 27% reduction in melanin content in the lesionalarea. Therefore siRNA agents can be used as tyrosinase inhibitors in melasma and also in melanoma safely as an alternative to traditional topicals.[84]

Anti Estrogen and anti VEGF

Estrogen, VEGF and angiogenesis are also important factors and root cause of pathogenesis of melasma. Therapeutic agent which can down regulate the expression of these factors consisting of an anti-estrogen and VEGF inhibitor would possibly downregulate melanosynthesis. Anti-neoplastic agents with estrogen receptors and VEGF inhibitors are already in use in oncology as systemic drugs. The systemic tomoxifen or raloxifene is an estrogen receptor modulator and anastrozole or letrozole or exemestane as an aromatase inhibitor. Bevacizumab is a known VEGF inhibitor. Hence a topical formulation with anti estrogen and VEGF growth factors may be another useful addition to melasma therapy.[85]

ORAL THERAPY

Tranexamic Acid (TXA)

Tranexamic acid reduces pigmentation of the face melasma by inhibiting the plasminogen system. It interferes with the interaction of melanocytes and keratinocytes. The oral tranexamic acid was explored for the treatment of intractable melasma. In the first phase 250 mg of tranexamic acid tablets were prescribed to 74 patients two times a day for a span of 24 weeks. In second phase patients were followed for 24 weeks after the treatment. Two physicians independently assessed the outcome of follow up. Four levels of efficacy were considered as benchmark. Excellent, good, fair, and poor. Six months post treatment, the efficacy results were excellent in 8 (10.8%), good in 40 (54%), fair in 23 (31.1%), and poor in 3 (4.1%). Side effects such as disturbance in digestivesystem (5.4%) and infrequent menstruation (8.1%) were observed, but no severe complications were found. The recurrence of melasma was observed in 7 (9.5%). [86] Additionally a study was done to see the efficacy of two different modalities with different mechanism of actions, oral TXA and topical therapy on the face. Twenty fivepatients were selected and prescribed 240 mg of TXA tablets twice daily in combination with alreadyproven tropical therapy. It significantly reduced ($P < 0.01$) the mean MASI score after tranexamic acid treatment. Mean improvement observed was 69%. Follow up was done for 24 weeks. It was concluded that oral tranexamic acid at lower doses can be given as an adjunct to topical is safe in refractory melasma.ss[87]

Pycnogenol (PYC)

A French maritime Pine bark extract from *Pinus pinaster* bark is a safe and evidence based premium ingredient. It is a herbal extract rich in several bioflavonoids with various applications in different clinical pharmacology.It'sa blend of procyanidins with multiple therapeutic applications. It retains skin moisture and elasticity and increases skin lightening. PYC is several times more powerful than vitamin E and vitamin C. It also reprocess vitamin C and reinvigorate vitamin E. It increases the endogenous antioxidant enzyme system and also protects against UV rays. A 30 days clinical trial was done in which 25 mg tablet of PYC was given three times a day. The assessments were done objectively using clinical parameters erythema index, pigmentary intensity index, routine blood and urine index. Excess melanin synthesis was controlled along with cell viability. Thus, it was concluded to be safe, effective & it inhibits the tyrosinase activity. [88] The efficacy, safety and tolerability of oral dose of 75 mg PYC was tested on 44 women. It was to be taken orally twice a day for 60 days against a control group where PYC 75 mg was given in association with the triple combination at night and both the groups were given broad-spectrum sunscreen SPF 50 for the treatment of facial melasma for 60 days. All diagnostic parameters, mMASI score, MELASQoL showed reduction in pigment. mMASI score was 49% for PYC and 34% for Placebo. GAIS improvement was 86% in PYC group against the 55% in control group with no adverse event; PYC is safe with no side effects. It was found to increase the efficacyof topical sunscreen. [89]

***Polypodium leucotomos* (PL)**

The Polypodium*leucotomos*(PL) is an effective photo protective agent in melasma as an adjunct therapy. Polypodium is a fern of the Polypodiaceae family. Its multifunctional hypopigmenting activity has made it a successful oral photoprotectant. The efficacy of PL 240 mg was assessed in a randomized, placebo-controlled study of 40 patients. One group was given oral 240mg T.I.D for a span of 12 weeks versus placebo in the second group. All subjects were prescribed sunscreen with SPF 55.Primary assessment was objective with calorimeter and secondary assessment was done with MASI score and quality of life. The Improvement in PLE group 28.8% was more than placebo group with 13.8%. [90] In a recent double-blind, placebo-controlled trial the ability to down regulate hyperpigmentation was explored. Patients were selected randomly and oral PL 240 mg tablet was prescribed B.I.S for a span of 12 weeks against placebo control. Subjects in both the groups applied topical broad spectrum sunscreen and 4% hydroquinone cream. MASI score of only PLE treatedsubjects demonstrated significant reduction in day 56 and 84 of treatment. [91] The extract of PL was also studied for its photo protection property. This antioxidantextract naturally produced from bark when applied topically on the skin or taken orally inhibits Free radical and super oxide anion production prompted by sun radiations. It prevents DNA damage and downregulates the expression of COX-2 (cyclo-oxygenase 2), AP1 and NF-κB induced by UV radiations protecting endogenous skin natural antioxidant enzyme systems likesuper-oxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), or work as non-enzymatic popular antioxidants like amelatonin, glutathione, uric or lipolic acid, and bilirubin. Its cellular level photo protective effects significantly reduce apoptosis and necrosis impeding extracellular matrix re-modelling.Additionallymode of action includes up-regulation of expression of p53 suppressor gene and modification of inflammatory cytokines. These molecular and cellular effects inhibit photoaging and carcinogenesis. [92]

Energy Devices

Q switched Nd YAG Laser

Pulsed Dye laser

Pro-yellow laser 577nm
Copper bromide Laser
RFMicro needling
Micro-needling
RF Micro-needling with Topicals

LASER DEVICES

There are very few studies on lasers in melasma. It does require more clinical research. Lasers work on the principal of selective photo thermolysis. There are three main chromophores in the skin. Haemoglobin. melanin and water. All the three have different absorption spectra. They selectively absorb different wavelengths of electromagnetic radiation. This allows physicians to treat large number of skin problems. Therefore complete understanding of laser basics can enhance the results of a dermatologist working on melasma. The Q switched Nd Yag laser (QSNY), Pico second Q switched Nd Yaglaser and Vascularlaser are useful in the management of pigmented lesions. Histological studies have found that cutaneous vasculature is increased in melasma lesions as compared to surrounding normal skin, which also proves that expression of VEGF in increased in melasma. [17] Pulse dye laser, new diode lasers giving pure yellow light like Pro-yellow 577,copper bromide laser with dual wavelength of 578 and 532 nm wavelength developed for vascular lesions also work on vascularity in melasma and PIH. It enhances the treatment outcomes of melasma. Lasers can treat pigmented skin lesions. The tissues having chromophores have specific thermal absorption and light absorption coefficient.The lasers work on the principal of selective photo thermolysis protecting the surrounding tissue. [93] Accordingly abnormal derma cosmetic conditions need light or laser therapy which including,hair removal, port wine stains or vascular birth marks, telangiectasias, hypertrichosis, tattoos and pigmented lesions, solar lentigines, lentiginous nevi, café -au-lait macules. Laser and light therapies can be added to conventional therapy of creams to enhance the results of refractory dermatological problems and can be utilized cautiously for intractable melasma. Hyperpigmentation should be treated with lower fluence to avoid irritating melanocytes which can cause post inflammatory hyperpigmentation of the face. Low-fluence 1064-nm Q-switched neodymium-doped yttrium aluminum garnet (Q switched Nd YAG) laser for melanocytic lesions. Vascular lasers like Pulse dye laser (dye based) and Diode pumped lasers generating pure yellow 577-595 nm wavelength for vascular lesions.

Mechanism of action

QSND laser explodes the pigment melanin in melanocytic lesion which gradually gets cleared with lymphatic drainage. It produces high peak power laser beams with very short pulse in nanosecond duration. The frequency of pulse is one million times that of other laser devices used in dermatology.

PDL Vascular Laser and Diode pumped Laser having wavelength of 577-595 nm stop neogenesis of capillaries and coagulates them.

Q switched Nd: YAG (QSNY) versus Pulse dye laser (PDL)

Two different laser technologies QSNY versus PDL were compared for hyperpigmentation. Single blind split face study was done on 17 patients having melasma. Standard method of selection and guidelines were followed. Total of 9 treatments of QSNY were done at an interval of one week and 3 treatments of vascular laser PDL was done at 0 week, 4 week and 8 week only on one half of face. Standard evaluation techniques MASI score and polarized dermoscopic images were part of evaluation to see dilatation of capillaries. Hyperpigmentation was evaluated at 0, 4 and 8 week after the treatment. Protocol designed for Q switched Nd YAG 1064/532 was spot size of 7 mm, laser energy at 1.2- 2.0 joules/cm2 at a speed of 10 Hertz. Mild erythema was the endpoint of treatment. Each face was given 5 to 7 passes. Protocol of 595 nm PDL was 7-8 Joules/cm2 energy with 20 ms pulse duration, spot size 7 mm and 2 or 3 passes. Patients were instructed to use sunscreen, not to use any lightening creams or any other cosmetic and avoid exposure to sun. Evaluation of improvement was done at week 8. Seven out of 17 (41.2%) patients who showed visibly widened capillaries on dermoscopic images, MASI score of both groups decreased significantly. The patients treated with only Q Switched Nd Yag did not show much improvement thence proved that combination of QSNY and PDL worked better. [94]

Fractional Pico Q switched Nd: YAG laser -1064/532nm

Picosecond Qswitched laser works on high peak power in giga bytes and pulses in picoseconds varying from 300-500 ps.The study was conducted on 20 Asian patients to demonstrate the efficacy and safety of fractionatedpico laser in treatment of melasma of face and rejuvenation of skin. Twenty patients included were of skin type III-IV and in age group 52-61years. All the subjects were exposed to laser therapy 9 times in 4 -6 weeks that is one treatment every 5 days. MASI score, IGAS and photography were tools used to assess improvement. Treatment satisfaction was reported in 14 (70%) patients. Baseline mMASI score of 10.8 got reduced to 2.7 in 6 weeks and 3.6 in 12 weeks ($P < 0.01$) after the therapy. Skin

rejuvenation was moderate in 70% of patients at 6 weeks after the therapy. Temporary erythema and edema was the only side effect. No hypo-or hyperpigmentation was observed. Hence fractionated non-ablativePicosecond Q switched Nd: YAG 1064 nm laser was effective and safe in treatment of melasma and skin rejuvenation. [95]

Vascular Diode Laser

A major clinical characteristic of melasma is hyperpigmented patches, but there are several hypotheses supporting angiogenetic factors that are related to some types of melasma. The environmental factors like UV radiation, infection or allergic reactions do affect & alter gross structure and functional role of the dynamic network of blood vessels in skin. Recently it has been suggested that there might be interaction between cutaneous vasculature and melanocytes which may be the cause of hyperpigmentation in epidermis with dermal components playing a crucial role. Kim et al [17] studied the vascular characteristics of 50 Korean women. He studied the expression of Vascular Endothelial Growth Factor (VEGF), VIII A factor related antigen in melasma. It was found through immunochemistry that the number of blood vessels increased and enlarged as compared with per-lesional normal skin.Increase in vessel size and density due to over expression of VEGF which stimulates the release of arachidonic acid, phosphorylation & activation of cytosolic phospholipase A2. It can be assumed that metabolites of arachidonic acid pathways may affect melanogenesis. It is also possible that UV radiations stimulate endothelial cells to release cytokines and plasminogen which might be the cause of hyperpigmentation. This has further given directions to scientists to look for new approaches to treat melasma which can regulate the VEGF hence neogenesis.

Pro-yellow 577 Vascular Diode Laser

The clinical efficacy and safety has been explored with Quadro Star Pro-yellow 577 a diode pumped vascular laser. Its pulse duration was calculated to match the thermal relaxation time of cutaneous blood vessels and its wavelength to coincide with the third absorption spectral peak of oxyhaemoglobin, (578 nm β-peak), this treatment caused general coagulation with injury to papillary dermis that produces intravascular thrombus formation without epidermal damage and preservation of dermal appendages to a depth of 0.4-0.7 mm. All subjects were treated with scanning hand piece of Pro-yellow 577 with pulse duration 20-30 m sec, fluences 8-14 J/cm2, 80 % skin coverage for whole face. This protocol was given to reduce the expression of vascular endothelial growth factor (VEGF) receptors 1 and 2 and neuropilin, hence decrease the melanocyte stimulation. The reduction of pigmentation with normalization in texture and colour of the treated skin was observed. Hence Pro-yellow 577 can treat safely all pigmentation having vascular structure whereas 532 can cause hyperpigmentation and hypopigmentation in skin type IV–VI. [96]

Copper bromide laser

Copper bromide laser is laser which produces two wavelengths of yellow light 578 nm and 532 nm simultaneously. A split face study was conducted on 20 patients of melasma. At the start of phase 1 triple combination cream was applied to all the subjects on the entire face daily once a day for 4 weeks. Next phase subjects were randomly selected for half face treatment with the copper bromide laser and contralateral face continued to receive daily application of the topical cream for 3 additional months. Four sessions of copper bromide laser were given at weeks 4, 6, 9 and 12. The yellow light at 578nm and green wavelength at 532 nm simultaneously produced at a ratio of 9:1. Protocol was fixed at fluence 12 J/cm2, 0.6 mm contact tip; and 1 pass with 1 mm spot size. Fluence was progressively increased, the emission time was 50 to 60 milliseconds and the off time was 70 milliseconds, with 7.7 to 8.3 pulses per second. The endpoint was erythema and a slight graying of the lesions. Follow-up visits were conducted at 3 and 6 months. The patient's MASI score at 6 months after the end of treatment & laser confocal microscopy was used to evaluate the improvement of the lesions that were treated between the baseline visit and 6 months after the end of the treatment. Triple combination Kligman's cream was found to be more effective than Laser. [97]

RF Micro needling (RFMN)

Comparative split face study of RF micro needling (RFMN) with laser toning and without laser toning was conducted on fifteen patients with melasma. Patients received five treatment sessions of laser toning and RFMN on the right half of the face, and laser toning only on the contralateral face. Objective evaluation was done using the colorimeter score; clinical assessment was done with the pigmentation and severity index (PSI) score, and the patient's overall assessment. Additionally, skin biopsy study was performed with an electron microscopy. Right face receiving mix of two therapy showed significant decreases in the hexameter and PSI score after five treatment sessions than the contralateral face receiving laser toning alone. There were no side effects noticed. Biopsy study reported increased number of vacuolar changes and increased loosening in binding of melanocytes and adjacent epidermal cells after combination

therapy. Therefore, addition of RF micro needle technique can improve the outcome of thetreatment of melasma safely. [98]

Micro-needling

The synergistic effect of micro-needling pen with topical therapies was evaluated from 12 studies. Different skin formulated serums with added ingredients TXA, ascorbic acid, and platelet rich plasma. Some formulations of serums included hydroquinone and some were without hydroquinone. The synergy of skin topicals with micro-needling reduced the excess intensity of pigment in melasma. The best outcome of therapy was seen after a span of 12 weeks compared to topical therapy alone. Patients did not feel the micro prick pain of micro-needling during the course of trials. Erythema was the only side effect observed. Accordingly micro-needling pen is a useful device to be added to treatment of melasma in synergy with topical serums containing depigmenting agents. [99]

Sunscreen /sunblock

Sunscreen offer protection from UVA, UVB and visible light. Sunscreens is added as an adjunct therapy to enhance the outcome of treatment of hyperpigmentation of face and avoid further damage to skin of melasma and PIH.[100]Additional studies were conducted on 20 volunteers with skin type IV-VI to explore the effect of Visible light VL(400-700nm)and combination of VL+UVA1(340-400nm) on pigmentation and delayed tanning. There were two electromagnetic radiation sources used for irradiation. Devices to assess the outcome were confocal microscopy, skinbiopsies. Colorimeter and histological studies with different stains. It was found that both visible light and mix radiationof (UVA1+VL) initiate pigmentation but it was darker with visible light than with combination of(VL+UVA1). Also both the pigmentations were different in terms of intensity and darkness.Hence it was concluded that a good broad spectrum sun protection is required as part of treatment to manage the pigmentation aggravated with sun exposure.[101] Additional study demonstrated extent of photodamaging effects of two single wavelengths located at both edges of the visible spectrum: at 415 nm (blue violet line) and at 630 nm (red line). Visible light radaiationspectrum is wide and all wavelengths of this spectrum do not have same effect on skin. Hence the pigmenting effect was assessed at 415 nm and 630 nm independently. Pigment intensity was enhanced with an exposure to 415nm and not with 630 nm. It was surprising to see erythema which is generally expected only with UVB spectrum (280-315) .It was also observed that wavelengths of 630 nm (red light) far edge of visible spectrum is not as harsh on skin as shorter wavelengths of 415nm(violet blue light) of the lower edge of visible spectrum which enhance the pigment intensity more. This increased pigmentation continues till three months. The results of treatment of melasma patients can be enhanced with good broad spectrum sun protection cream which can cover the spectrum of 310-400nm and 400-700 simultaneously.[103] Additional study while designing the guidelines for new sun protection product for photodamaged skin a study was done exposing the skin to mix of visible light and minimal ultraviolet light (UVA1).Ten subjects were selected with skin type IV–VI. The back of all these subjects were exposed to two different wavelengths of light and two sources. First source of exposure was pure VL and second source was a mix of VL with less than 0·5% UVA1 (VL+UVA1).Aim was to observe the influence on skin when exposed to two different spectrums of wavelengths. Tools to assess the response were photography, Investigator's Global Assessment, colorimetry and spectroscopy. Assessment was performed at the start of irradiation at 0 week, 1day, 7 days and 14 days after exposure. Pigmentation was observed with both light sources visible light (VL) and ultraviolet A (UVA !). Pigmentation of skin increased more with (VL+UVA1) than with pure VL alone. The interplay between skin and radiation was observed in pure VL sites, but not at (VL+UVA1). The hyperpigmentation is highly influenced by band of spectrum of light the facial skin is exposed to. Erythema was observed on the (VL+UVA1) side, but not on the pure VL side. [102] Visible light also plays a role in stimulating pigmentation. The results of treatment of melasma patients can be enhanced with good broad spectrum sun care which can cover the spectrum of 310-400nm and 400-700 nm simultaneously. [103] UVA1 radiations are constantly following the same pattern all around the year and gets absorbed by skin chromophores. It influences all layers of skin. It creates oxidative stress and changes at biological level and molecular levels. It can cause inflammation, mutations and breakdown of cells resulting in excess pigmentation, photosensitivity, skin cancer and immunosuppression. Hence radiation and successive addition of pollution cause structural damages and biochemical changes in the skin. Some of these changes are irreversible. Protecting the skin and maintainining its core structure and functionality is a matter of concern and a challenge.[104]

Oxidative stress

It has been observed clinically oxidative stress in melasma patients get elevated because of imbalance between oxidant and anti-oxidants. Two groups of 50 melasma patients and 50 healthy volunteers were incorporated in the study to evaluate the role of oxidative stress in melasma. The melasma patients were diagnosed clinically and the patients were evaluated by Melasma Area Severity Index. All the patients in

both groups underwent the assessment of Super-oxide dismutase (SOD), glutathione peroxidase (GSH-Px) enzyme activities and malondialdehyde, nitric oxide, protein carbonyl levels.Theantioxidant enzyme activities were significantly higher in the patient group in comparison with the control group ($p < 0.001$). Protein carbonyl levels were significantly lower in the patient group ($p < 0.001$). These results enhanced the knowledge of skin disorder melasma and its pathogenesis. [105].

TABLE 1: Role of UV generated pathogenic factors in causation of melasma

S.No	Pathogenic factor	Mechanism of action and its effect
1.	(MC1-R) Melanocyte Stimulating hormone Receptors	**Action**: UVR exposure upregulates the α Melanocortin -1 receptors (MC1-R) on melanocytes. There is transformation of radiant energy into chemical energy. **Effect**: The increase in MC1-R increase the high binding affinity of hormone hence increase melanosynthesis and cAMP.[5] The lesional skin has increased levels of α MSH.[6]
2.	POMC	**Action**: Proopiomelanocortin (POMC) split to produce peptides, α MSH & adrenocorticotropic hormone (ACTH). **Effect:** Peptides bind to melanocytes and activate MC1-R which increase levels of Protein Kinase A (PKA). This phosphorylates cAMP response element (CREB).[7] Hence increase melanogenesis.
3.	CREB	**Action:** CREB (cAMP -response element binding protein) is transcription factor for MITF **Effect**: MITF is the key factor responsible for tyrosinase enzyme regulation for various steps of melanogenesis.[7]
4.	p53	**Action:** The tumor suppressor protein p53 upregulates POMC **Effect**: POMC protein also increases transcription of hepatocyte nuclear transcription factor-1 alpha (HNF-1alpha), which activates tyrosinase downstream to increase melanin.[7]
5.	Endogenous DAGs (1,2-Diacylglycerol)	**Action**: UV radiation stimulate phospholipase C and D (PLC and PLD) pathways & produce endogenous DAGs so called second messenger, from plasma membrane phospholipids of melanocytes. **Effec**t: These DAGs go on to activate tyrosine and therefore increase melanogenesis in cultured human melanocytes and keratinocytes.[8].
6.	Keratinocyte	**Action:** Ultraviolet B exposure can stimulate keratinocytes to increase melanocyte. **Effect**: Keratinocytes secret various growth factors, cytokines, and hormones including inducible nitric oxide synthase (iNOS).[9]
7.	Visible light(VL)	**Action**: Visible light may up-regulate melanogenesis in melasma, especially in darker skin types (Fitzpatrick types IV-VI). **Effect**: Visible light interacting with the opsin 3 sensor hence melanogenesis.[10]
8.	Solar elastoses	**Action**: The collection of unusual elastic tissue in the dermis. **Effect**: Increased tryptase from mast cells can activate the production of elastin.[11]
9.	COX-2	**Action**: UV exposure cause dermal inflammation (DI) **Effect**: DI increase level of COX-2 and prostaglandins and stimulate melanocytes to increase melanogenesis.[12]
10	C. Kit	**Action**: Dermal inflammation activates fibroblasts. **Effect**: Levels of stem cell growth factor receptor, also known as c-kit, are also upregulated in melasma lesions.[13]
11	Plasmin	**Action**: UVB irradiation up-regulates plasmin production by keratinocytes. **Effect:** This enzyme leads to higher levels of arachidonic acid and alpha- MSH and therefore stimulates the melanin synthesis pathway.[14]
12	Mast cells	**Action**: UV exposure increase numbers of mast cells in human epidermal cells **Effect:** Increased mast cells release histamine, leading to inflamed skin. (downstream effect) Histamine binding at the H2 receptor activates the tyrosinase pathway hence melanogenesis.[15]
13	Mast cells	**Action:** UVR increases the production of mast cell tryptase which activates Matrix metallo-proteinase (MMP) precursors. **Effect**: The active enzyme MMP degrade type IV collagen and damage the basement membrane. Granzyme B directly released by mast cells further damage extra cellular matrix(ECM).[11]
14	Mast cells VEGF, 2FGF-2 & TGF-B .	**Action**: Mast cell induce hypervascularisation secreting proteins such as vascular endothelial growth factor (VEGF), Fibroblast growth factors 2(FGF),transforming growth factors_B (TGF-B). **Effect**: The angiogenic factors increase the size, density and dilatation of vessels in affected skin. [17,18]

15	Hormones	**Action**: Oestrogen receptors in the dermis and progesterone receptors in the epidermis of melasma lesions increase. **Effect**: Binding of estrogen to its receptors on melanocytes and keratinocytes can activate tyrosinase and MITF pathways to activate melanin production.[19.20]
16.	PDZ domain protein kidney 1(PDZK1).	**Action:** PDZK1increase **Effect:** Upregulated PDZK1 which regulates ion exchangers, in melasma lesions. could help mediate interactions between oestrogen&ion exchangers to increase melanogenesis and melanosome transfer.[21]
17.	Basement Membrane Damage	**Action**: UV damage activates MMP2 and MMP9. **Effect**: Upregulated enzymes degrade type IV and VI collagen in the basement membrane.[11]
18.	Cadherin 11	**Action**: Cadherin 11, an adhesion molecule that is upregulated in melasma skin **Effect**: Cadherin 11, can then mediate interaction between fibroblasts and melanocytes and promote melanogenesis.[22]
19.	Cadherin 11	**Action**: Cadherin 11 upregulates MMP1 and MMP2 expression. **Effect**: Collagen degradation and increase elastotic material.[22]
20.	Basement membrane damage	**Action**: Frequent recurrence of melasma **Effect**: Melanocytes and melanin granules move down into the dermis. Therefore recurrence of melasma. Melasma skin is thicker with curled elastin fibers.[11]
21.	Defective barrier function. Biopsy study on 11 subjects	**Effect** Skin is characterized by impaired stratum corneum integrity and a delayed barrier recovery rate. Cutaneous biophysical characteristics of melasma, MI, EI & stratum corneum hydration and rate of TEWL was higher in lesional skin than in perilesional normal skin. .The barrier recovery rate was delayed. stratum corneum thinning observed for lesional skin.The expressions of PPAR-α and ALOX15B are found to be variable.[23]

Table 2: Inhibition of melanin production in MelanoDerm™ skin models by 4-butylresorcinol, kojic acid, arbutin and hydroquinone Melanin content of skin models was determined after 13 days of cultivation in the presence of various inhibitor concentrations.
Data represent the mean of five independent experiments.[43]

s.no.	Name of Ingredients	IC50	% of inhibition of Melanin production
1.	4n butyl resorcinol	13.5 µmol/L	85-90%
2.	Hydroqinone	40 µmol/L	40-45%
3.	Kojic acid	> 400 µmol/L	75-80%
4.	Arbutin	> 5000 µmol/L	45-50%

Table 3: Analogs of resorcinol IC 50 for each analogue required for tyrosinase inhibition. [43]

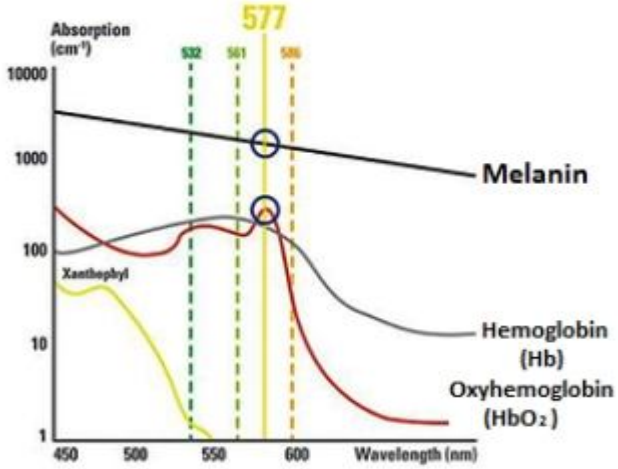
Name of Ingredients	IC50
4n butyl resorcinol	21µmol/L
4-hexylresorcinol	94µmol/L
4-phenylethylresorcinol	131µmol/L

Table 4:Various mechanism of actions of resveratrol in inhibiting melanogenesis in melasma

S.No.	Mechanism	Action
1.	Direct Inhibitor	Direct tyrosinase inhibitor, due to its ability to serve as an alternative substrate for tyrosinase.[62]
2.	Indirect inhibitor	Indirect inhibitor, due to its ability to inhibit transcription of tyrosinase or regulate it post-transcriptionally.[63]
3.	Transcription Factor MITF	MITF the most essential regulator and transcriptional activator of more than 25 genes in pigment cells.It regulates complete melanocyte cycle, enzymes expression & structural proteins. Encodes melanosome-localised responsible for melanin synthesis melanosome biogenesis and transport.[64]
4.	Basement membrane	It can affect keratinocytes by regulating their inflammatory processes, protecting them from oxidative damage, and repairing the basement membrane .[65]
5.	Activation of FOXO3	Resveratrol also inhibits melanogenesis through the activation of fork head box O3 (FOXO3) without surtuin 1 (SIRT1) activation.[65]
6.	Post transcription	Sphingosine-1-phosphate (S1P) interfered with melanogenesis via ERK-activated transcription regulation followed by MITF down regulation and as a matter of interest resveratrol stimulated S1P signalling in keratinocytes.[66,67]
7.	cAMP,PKC and	Resveratrol decreases transcription of tyrosinase by regulating cAMP, PKC, and MAP

	MAP kinase pathways	kinase pathways.[68]
8.	Retention of immature tyrosinase	Post-transcriptional effects on tyrosinase. Retention of immature tyrosinase in the endoplasmic reticulum by resveratrol reduces the levels of fully processed tyrosinase.[69]
9.	Map kinase pathway	Resveratrol suppressed antimycin A-mediated reactive oxygen species (ROS) production in melanocytic cells. Furthermore, resveratrol can also decrease melanogenesis by regulating the MAP kinase pathway, which is another important signalling pathway in melanogenesis.[70]
10.	Inflammatory Disorder	Resveratrol protects against inflammatory disorders by affecting arachidonic acid metabolism by reducing inflammatory mediators produced by keratinocytes, resveratrol prevents inflammation-induced melanogenesis.[71]
11.	Basement membrane	It repairs basement membrane by Increasing integrin α6 and p63 expression and, thus protects the effects by checking the differentiation of interfollicular epidermal cells.[72]
12.	Penetration	Topically applied resveratrol penetrates the skin in a gradient fashion and is able to maintain its antioxidant skin permeation and anti-inflammatory efficiency in the skin.[73]
13.	Antioxidant	Resveratrol has beneficial effects on redox balance not only through its direct antioxidant properties but also by the up-regulation of endogenous antioxidant pathways through activation of the nuclear factor erythroid 2-related factor (Nrf2) pathway.[74]
14.	Autophagy	Autophagy is a regulatory signal of hyperpigmentation in melanocytes. autophagosomes generation in melanocytes is controlled for monitoring melanogene -antimelanogenesis activity. Antimelongenic activity of resveratrol has direct relationship with inhibition of autophagy.[75]

Figure1: Absorption Curve of the main chromophore



The 577nm wavelength of the Pro-yellow laser is effectively absorbed by both melanin (pigmentation) and oxyhaemoglobin (blood vessels).Hence can work on pigmentation and vascular lesions.

CONCLUSION

The review of above studies demonstrates clearly that monotherapy is not enough to give satisfactory depigmenting effect and long term efficacy in Melasma. Polarized dermoscopy imaging is an important diagnostic system to see changes under the skin in addition to clinical photography with before and after pictures. Melasma is recalcitrant. Delay in recurrence is possible with integration of technologies as per patient'sneed. Hence to meet the expectation of patients it is important to combine the newer technologies with conventional treatment. Synergy of technologies selected should be able to regulate the transcription, inhibit the activity of tyrosinase and TPR1 proteins, paracrine regulation of melanogenesis, signals for melanocyte activation. Tyrosinase is the key regulator of melanin production and the most prominent target for inhibitors of hyperpigmentary disorders. Dermoscopic images are good guide to customize the treatment because of availability of various modalities along with clinical research. Plateau is part of all therapeutic interventions eventually. Treatment does require sequential modification in therapy system to see incremental improvement. It ensures stability and satisfies the curiosity of patients. Lasers are adjunct in melasma therapy and adding vascular lasers in patients having increased vascularity in melasma, PIH, sun damaged skin and Q switched Nd YAG Lasers at lower fluences help in breaking the pigment so that it can be released from body through lymphatic drainage.Hence lasers can give stability

to treatment results but require proper protocols and more clinical studies. UV protection with sunblock and sunscreens along with oral sun protection plays an important role in the management and efficacy of the treatment while the therapy is in process. Chemical, natural and molecular formulations can be used in rotation in the interest of better results.

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REFERENCES

1. Goukassian DA, Eller MS, Yaar M, Gilchrest BA. (1999). Thymidine dinucleotide mimics the effect of solar simulated irradiation on p53 and p53-regulated proteins. J Invest Dermatol ;112(1):25-31.
2. Lieu TJ, Pandya AG. (2012). Melasma quality of life measures. Dermatol Clin;30(2):269-80.
3. Zhu Y, Zeng X, Ying J, Cai Y, Qiu Y, Xiang W. (2022). Evaluating the quality of life among melasma patients using the MELASQoL scale: A systematic review and meta-analysis. PLoS One;17(1):e0262833.
4. RajanalaS, Maymone MBC, Vashi NA. (2019). Melasma pathogenesis: A review of the latest research, pathological findings, and investigational therapies. Dermatol Online J;25(10):90-93
5. Bolognia J, Murray M, Pawelek J. (1989). UVB-induced melanogenesis may be mediated through the MSH-receptor system. J Invest Dermatol;92:651-6.
6. Im S, Kim J, On WY, Kang WH. (2002). Increased expression of alpha-melanocyte stimulating hormone in the lesional skin of melasma. Br J Dermatol;146:165-7.
7. Videira IFS, Moura DFL, Magina S. (2013). Mechanisms regulating melanogenesis. An Bras Dermatol ;88:76-83.
8. Carsberg CJ, Ohanian J, Friedman PS. Ultraviolet radiation stimulates a biphasic pattern of 1,2-diacyglycerol formation in cultured human melanocytes and keratinocytes by activation of phospholipases C and D. Biochem J 1995;305:471-7.
9. Imokawa G, Yada Y, Morisaki N, Kimura M.(1999). Biological characterization of human fibroblast-derived mitogenic factors for human melanocytes. Biochem J;330:1235-9.
10. Passeron T, Picardo M. (2018). Melasma, a photo aging disorder. Pigment Cell Melanoma Res ;31:461-5.
11. Kwon S,Hwang Y, Lee S, Park K. (2016). Heterogeneous pathology of melasma and its clinical implications. Int J Mol Sci;17:824.
12. Gledhill K, Rhodes LE, Brownrigg M, et al. (2010). Prostaglandin-E2 is produced by adult human epidermal melanocytes in response to UVB in a melanogenesis-dependent manner. Pigment Cell Melanoma Res ;23:394-403.
13. Kang HY, Hwang JS, Lee DJ, et al. (2006). The dermal stem cell factor and c-kit are over expressed in melasma. Br J Dermatol;154:1094-9.
14. Taraz M, Niknam S, Ehsani AH. Tranexamic acid in treatment of melasma: A comprehensive review of clinical studies. Dermatol Ther2017;30:1-8.
15. Malaviya R, Morrison AR, Pentland AP. Histamine in human epidermal cells is induced by ultraviolet light injury. J Invest Dermatol 1996;106:785-9.
16. Yoshida M, Takahasi Y, Inoue S. Histamine induces melanogenesis and morphologic changes by protein kinase A activation via H2 receptors in human normal melanocytes. J Invest Dermatol 2000;114: 334-42.
17. Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. J Dermatol Sci 2007; 46: 111-6.
18. Kwon S, Park K. Clues to the pathogenesis of melasma from its histological findings. J Pigment Disord2014;1:5
19. Jang, YH, Lee JY, Kang HY, Lee ES, Kim YC.Oestrogen and progesterone receptor expression in melasma: an immuno-histochemical analysis. J EurAcad Dermatol Venereol2010;24:1312-6.
20. Liberman R, Moy L. Estrogen receptor expression in melasma: results from facial skin of affected patients. J Drugs Dermatol 2008;7:463-5.
21. Lee AY. Recent progress in melasma pathogenesis. Pigment Cell Melanoma Res 2015;28(6):648-60.
22. Kim NH, Choi SH, Lee TR, Lee CH, Lee AY. Cadherin 11 involved in basement membrane damage and dermal changes in melasma. Acta DermVenereol2016;96:635-40.
23. Lee DJ, Lee J, Ha J, et al. Defective barrier function in melasma skin. J EurAcad Dermatol Venereol2012;26:1533-7.
24. Sheth VM, Pandya AG. Melasma: A comprehensive update: Part I. J Am Acad Dermatol 2011;65:689-97.
25. Van Scott EJ, Yu RJ. Control of keratinization with a-hydroxy acids and related compounds. Archives of Dermatology 1974;110(4):586-90.
26. Manjunath KG, Raghu MT, Yogendra M, Harish G. A clinical and therapeutic study of efficacy of 40% glycolic acid facial peels in melasma. Int J Res Dermatol 2018;4:136-41.
27. Baliña LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. Int J Dermatol 1991;30:893-5.
28. Kircik LH. Efficacy and safety of azelaic acid (AzA) gel 15% in the treatment of post-inflammatory hyperpigmentation and acne: A 16-week, baseline-controlled study. J Drugs Dermatol 2011;10(6):586-90.

29. Dayal S, Sahu P, Dua R. Combination of glycolic acid peel and topical 20% azelaic acid cream in melasma patients: Efficacy and improvement in quality of life. J Cosmet Dermatol 2017;16(1):35-42.
30. Faghihi G, Taheri A, Shahmoradi Z, Nilforoushzadeh MA. Solution of azelaic Acid (20%), Resorcinol (10%) and Phytic Acid (6%) Versus Glycolic Acid (50%) peeling agent in the treatment of female patients with facial melasma. Adv Biomed Res 2017; 22;6:9.
31. Bhardwaj V, Sharma K, Maksimovic S, Fan A, Adams-Woodford A, Mao J. Professional-Grade TCA-lactic acid chemical peel: Elucidating mode of action to treat photoaging and hyperpigmentation. Front Med (Lausanne) 2021;8:617068.
32. Cucé LC, Bertino MC, Scattone L, Birkenhauer MC. Tretinoin peeling. Dermatol Surg 2001;27(1):12-4.
33. Griffiths CE, Finkel LJ, Ditre CM, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. Br J Dermatol. 1993;129(4):415-21.
34. Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN, Voorhees JJ. Topical retinoic acid (tretinoin) for melasma in black patients. A vehicle-controlled clinical trial. Arch Dermatol. 1994 Jun;130(6):727-33.
35. Kim HJ, Moon SH, Cho SH, Lee JD, Kim HS. Efficacy and safety of tranexamic acid in melasma: A Meta-analysis and systematic review. Acta DermVenereol 2017;97(7):776-81.
36. Kim SJ, Park JY, Shibata T, Fujiwara R, Kang HY. Efficacy and possible mechanisms of topical tranexamic acid in melasma. Clin Exp Dermatol 2016;41(5):480-5.
37. Desai S, Ayres E, Bak H, Manco M, Lynch S, Raab S, et al. Effect of a Tranexamic acid, kojic acid, and niacinamide containing serum on facial dyschromia: A clinical evaluation. J Drugs Dermatol 2019;18(5):454-9.
38. Lee DH, Oh IY, Koo KT, Suk JM, Jung SW, Park JO, et al. Reduction in facial hyperpigmentation after treatment with a combination of topical niacinamide and tranexamic acid: A randomized, double-blind, vehicle-controlled trial. Skin Res Technol 2014;20(2):208-12.
39. Kim DS, Kim SY, Park SH, Choi YG, Kwon SB, Kim MK, et al. Inhibitory effects of 4-n-butylresorcinol on tyrosinase activity and melanin synthesis. Biol Pharm Bull 2005;28(12):2216-9.
40. Shimizu K, Kondo R, Sakai K. Inhibition of tyrosinase by flavonoids, stilbenes and related 4-substituted resorcinols:structure activity investigations. Planta Med 2000; 66:11-5.
41. Arung ET, Shimizu K, Kondo R. Artocarpus plants as a potential source of skin whitening agents. Nat Prod Commun2011;6:1397-1402.
42. Kang M, Park SH, Oh SW, Lee SE, Yoo JA, Nho YH, et al. Anti-melanogenic effects of resorcinol are mediated by suppression of cAMP signaling and activation of p38 MAPK signaling. BiosciBiotechnolBiochem 2018;82(7):1188-96.
43. Kolbe L, Mann T, Gerwat W, Batzer J, Ahlheit S, SchernerC,et al. 4-n-butylresorcinol, a highly effective tyrosinase inhibitor for the topical treatment of hyperpigmentation. J EurAcad Dermatol Venereol. 2013;27 Suppl 1:19-23.
44. Huh SY, Shin JW, Na JI, Huh CH, Youn SW, Park KC. The efficacy and safety of 4-n-butylresorcinol 0.1% cream for the treatment of melasma: A randomized controlled split-face trial. Ann Dermatol 2010;22(1):21-5.
45. Madan Mohan NT, Gowda A, Jaiswal AK, Sharath Kumar BC, Shilpashree P, Gangaboraiah B, et al. Assessment of efficacy, safety, and tolerability of 4-n-butylresorcinol 0.3% cream: An Indian multicentric study on melasma. Clin Cosmet Investing Dermatol 2016;9:21-7.
46. Kim SY, Park KC, Kwon SB, Kim DS. Hypopigmentary effects of 4-n-butylresorcinol and resveratrol in combination. Pharmazie2012;67:542-6.
47. Kwon SH, Yang JH, Shin JW, Park KC, Huh CH, Na JI. Efficacy of liposome-encapsulated 4-n-butylresorcinol and resveratrol cream in the treatment of melasma. J Cosmet Dermatol 2020;19(4):891-5.
48. Lima PB, Dias JAF, Cassiano DP, Esposito ACC, Miot LDB, Bagatin E, Miot HA. Efficacy and safety of topical isobutylamido thiazolyl resorcinol (Thiamidol) vs. 4% hydroquinone cream for facial melasma: an evaluator-blinded, randomized controlled trial. J EurAcad Dermatol Venereol 2021 ;35(9):1881-7.
49. Chatterjee M, Neema S, Rajput GR. A randomized controlled pilot study of a proprietary combination versus sunscreen in melasma maintenance. Indian J Dermatol VenereolLeprol 2021;88(1):51-8.
50. Ishioka W, Oonuki S, Iwadate T, Nihei KI. Resorcinol alkyl glucosides as potent tyrosinase inhibitors. Bioorg Med Chem Lett 2019;29(2):313-6.
51. Besouw M, Masereeuw R, van den Heuvel L, Levtchenko E. c
52. Mansouri P, Farshi S, Hashemi Z, Kasraee B. Evaluation of the efficacy of cysteamine 5% cream in the treatment of epidermal melasma: A randomized double-blind placebo-controlled trial. Br J Dermatol 2015;173(1):209-17.
53. Jeon HJ, Kim K, Kim C, Kim MJ, Kim TO, Lee SE. Molecular mechanisms of anti-melanogenic gedunin derived from Neem tree (*Azadirachta indica*) using B16F10 mouse melanoma cells and early-stage zebrafish. Plants (Basel). 2021;10(2):330.
54. Majeed M, Pineda RTV, Chan G , Gabriel T, Dayrit J, Pelayo CA, et al.Randomized, double-blind, placebo-controlled, comparative study. The safety and efficacy of 0.25%. tetrahydrocurcumin (turmeric) cream as depigmenting agent against 4% hydroquinone .HPC today 2010;3:44-46
55. Setiawati S, Ilyas F, Tabri F, Djawad K, Alam G. A comparison between 0.25% turmeric extract cream and grated turmeric for skin discoloration, Amer J Clin Exper Med 2017;5:50-5.
56. Draelos, ZD. (2015). A split-face evaluation of a novel pigment-lightening agent compared with no treatment and hydroquinone. JAAD 2015;72:105-7.

57. Mauricio T, Karmon Y, Khaiat A. A randomized and placebo-controlled study to compare the skin-lightening efficacy and safety of lignin peroxidase cream vs. 2% hydroquinone cream. J Cosmet Dermatol 2011;10(4):253-9.
58. Choi S, Lee SK, Kim JE, Chung MH, Park YI. Aloesin inhibits hyperpigmentation induced by UV radiation. Clin Exp Dermatol 2002;27(6):513-5.
59. Jin YH, Lee SJ, Chung MH, Park JH, Park YI, Cho TH, et al. Aloesin and arbutin inhibit tyrosinase activity in a synergistic manner via a different action mechanism. Arch Pharm Res 1999;22(3):232-6.
60. Ratz-Lyko A, Arct J. Resveratrol as an active ingredient for cosmetic and dermatological applications: A review. J Cosmet Laser Ther2018;21:84-90.
61. Na JI, Shin JW, Choi HR, Kwon SH, Park KC. Resveratrol as a multifunctional topical hypopigmenting agent. Int J Mol Sci 2019;20(4):956.
62. Fenoll LG, Rodriguez-Lopez JN, Varon R, Garcia-Ruiz PA, Garcia-Canovas F, Tudela J. Action mechanism of tyrosinase on meta- and para-hydroxylated monophenols. Biol Chem 2000; 381:313-20.
63. Lin CB, Babiarz L, Liebel F, Roydon PE, Kizoulis M, Gendimenico GJ, et al. Modulation of microphthalmia-associated transcription factor gene expression alters skin pigmentation. J. Investig. Dermatol2002;119:1330-40.
64. Vachtenheim J, Borovanský J. "Transcription physiology" of pigment formation in melanocytes: Central role of MITF. Exp Dermatol 2010;19(7):617-27.
65. Wang X., Zhang Y. Resveratrol alleviates LPS-induced injury in human keratinocyte cell line HaCaT by up-regulation of miR-17. Biochem. Biophys. Res. Commun2018;501:106-12.
66. Lee TH,Seo JO, Baek SH, Kim SY. Inhibitory effects of resveratrol on melanin synthesis in ultraviolet B-induced pigmentation in guinea pig skin. Biomol. Ther2014;22:35-40.
67. Kwon SH, Choi HR, Kang YA, Park KC. Depigmenting effect of resveratrol is dependent on FOXO3a activation without SIRT1 activation. Int J Mol Sci 2017;18:1213.
68. Park K, Elias PM, Hupe M, Borkowski AW, Gallo RL, Shin KO, et al. Resveratrol stimulates sphingosine-1-phosphate signaling of cathelicidinproduction.JInvestig Dermatol2013;133:1942-9.
69. Yasumoto K, Yokoyama K, Takahashi K, Tomita Y, Shibahara S. Functional analysis of microphthalmia-associated transcription factor in pigment cell-specific transcription of the human tyrosinase family genes. J Biol Chem 1997;272:503-9.
70. Newton RA, Cook AL, Roberts DW, Leonard JH, Sturm RA. Post-transcriptional regulation of melanin biosynthetic enzymes by cAMP and resveratrol in human melanocytes.J Investig Dermatol2007;127:2216-27.
71. Nguyen C, Savouret JF, Widerak M, Corvol MT, Rannou F. Resveratrol, potential therapeutic interest in joint disorders: A critical narrative review. Nutrients2017;9:45.
72. Shin JW, Choi HR, Nam KM, Lee HS, Kim SA, Joe HJ, et al. The co-expression pattern of p63 and HDAC1: A potential way to disclose stem cells in interfollicular epidermis. Int J Mol Sci2017;18:1360.
73. Alonso C, Marti M, Barba C, Carrer V, Rubio L, Coderch L. Skin permeation and antioxidant efficacy of topically applied resveratrol. Arch Dermatol Res2017;309:423-31.
74. Soeur J, Eilstein J, Lereaux G, Jones C, Marrot L. Skin resistance to oxidative stress induced by resveratrol: From Nrf2 activation to GSH biosynthesis. Free Radic Biol Med 2015;78:213-23.
75. Kim ES, Chang H, Choi H, Shin JH, Park SJ, Jo YK, et al. Autophagy induced by resveratrol suppresses alpha-MSH-induced melanogenesis. Exp. Dermatol2014;23:204-6.
76. Park J, Park JH, Suh HJ, Lee IC, Koh J, Boo YC. Effects of resveratrol, oxyresveratrol, and their acetylated derivatives on cellular melanogenesis. Arch Dermatol Res2014;306:475-87.
77. Shin NH, Ryu SY, Choi EJ, Kang SH, Chang IM, Min KR, Kim Y. Oxyresveratrol as the potent inhibitor on dopa oxidase activity of mushroom tyrosinase. BiochemBiophys Res Commun1998;243:801-3.
78. Zheng ZP, Zhu Q, Fan CL, Tan HY, Wang M. Phenolic tyrosinase inhibitors from the stems of *Cudraniacochinchinensis*. Food Funct 2011;2(5):259-64.
79. Zheng ZP, Tan HY, Wang M. Tyrosinase inhibition constituents from the roots of *Morus australis*. Fitoterapia 2012;83(6):1008-13.
80. Ryu JH, Seok JK, An SM, Baek JH, Koh JS, Boo YC. A study of the human skin-whitening effects of resveratryl triacetate. Arch Dermatol Res 2015;307(3):239-47.
81. Shen Z, Wang Y, Guo Z, Tan T, Zhang Y. Novel tyrosinase inhibitory peptide with free radical scavenging ability. J Enzyme Inhib Med Chem 2019;34(1):1633-40.
82. Hantash BM, Jimenez F. A split-face, double-blind, randomized and placebo-controlled pilot evaluation of a novel oligopeptide for the treatment of recalcitrant melasma. J Drugs Dermatol 2009;8(8):732-5.
83. Park J, Jung H, Kim K, Lim KM, Kim JY, Jho EH, et al. D-tyrosine negatively regulates melanin synthesis by competitively inhibiting tyrosinase activity. Pigment Cell Melanoma Res 2018;31(3):374-83.
84. Xiang Y, Zhao G, Zhang H, Guan D, Meng R, Zhang Y, et al. MITF-siRNA formulation is a safe and effective therapy for human melasma. Mol Ther. 2011;19:362- 371.
85. Cohen PR. Melasma treatment: A novel approach using a topical agent that contains an anti-estrogen and a vascular endothelial growth factor inhibitor. Med Hypotheses 2017;101:1-5.
86. Wu S, Shi H, Wu H, Yan S, Guo J, Sun Y, et al. Treatment of melasma with oral administration of tranexamic acid. Aesthetic Plast Surg 2012;36(4):964-70.
87. Tan AWM, Sen P, Chua SH, Goh BK. Oral tranexamic acid lightens refractory melasma. Australas J Dermatol. 2017;58(3): e105-e108.
88. Ni Z, Mu Y, Gulati O. Treatment of melasma with pycnogenol. Phytother Res 2002;16(6):567-71.

89. Lima PB, Dias JAF, Esposito ACC, Miot LDB, Miot HA. French maritime pine bark extract (pycnogenol) in association with triple combination cream for the treatment of facial melasma in women: a double-blind, randomized, placebo-controlled trial. J EurAcad Dermatol Venereol 2021;35(2):502-8.
90. Ahmed AM, Lopez I, Perese F, Vasquez R, Hynan LS, Chong B et al. A randomized, double-blinded, placebo-controlled trial of oral *Polypodium leucotomos* extract as an adjunct to sunscreen in the treatment of melasma. JAMA Dermatol. 2013;149(8):981-3.
91. Goh CL, Chuah SY, Tien S, Thng G, Vitale MA, Delgado-Rubin A. Double-blind, placebo-controlled trial to evaluate the effectiveness of *Polypodium leucotomos* extract in the treatment of melasma in Asian skin: A pilot study. J Clin Aesthet Dermatol 2018;11(3):14-9.
92. Gonzalez S, Gilaberte Y, Philips N, Juarranz A. Fernblock, a nutriceutical with photoprotective properties and potential preventive agent for skin photoaging and photoinduced skin cancers. Int J Mol Sci. 2011;12(12):8466-75.
93. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science 1983;220(4596):524-7.
94. Kong SH, Suh HS & Choi YS. Treatment of melasma with pulsed-dye Laser and 1,064-nm Q-Switched Nd:YAG Laser: A split-face study. Annals of Dermatology 2018;30(1):1-7.
95. Wong CSM, Chan MWM, Shek SYN, Yeung CK, Chan HHL. Fractional 1064 nm Picosecond Laser in treatment of melasma and skin rejuvenation in Asians, A prospective study. Lasers Surg Med 2021;53(8):1032-42.
96. Mohamed EM, Younes AH, Hussein GM. Efficacy of 577 nm pro-yellow laser in the treatment of melasma: A prospective split-face study. J Cosmet Laser Ther 2020;22(2):107-10.
97. Hammami-Ghorbel H, Boukari F, Fontas E, Montaudié H, Bahadoran P, Lacour JP, et al. Copper bromide laser vs triple-combination cream for the treatment of melasma: A randomized clinical trial. JAMA Dermatol 2015;151(7):791-2.
98. Jung JW, Kim WO, Jung HR, Kim SA, Ryoo YW. A face-split study to evaluate the effects of microneedle radiofrequency with Q-Switched Nd:YAG Laser for the treatment of melasma. Ann Dermatol 2019;31(2):133-8.
99. Bailey AJM, Li HO, Tan MG, Cheng W, Dover JS. (2022). Micro-needling as an adjuvant to topical therapies for melasma: A systematic review and meta-analysis. J Am Acad Dermatol;86(4):797-810.
100. Fatima S, Braunberger T, Mohammad TF, Kohli I, Hamzavi IH. (2020). The role of sunscreen in melasma and post inflammatory hyperpigmentation. Indian J Dermatol,;65(1):5-10.
101. Mahmoud BH, Ruvolo E, Hexsel CL, Liu Y, Owen MR, Kollias N, et al. (2010). Impact of long-wavelength UVA and visible light on melanocompetent skin. J Invest Dermatol;130:2092–7.
102. Duteil L, Cardot-Leccia N, Queille-Roussel C, Maubert Y, Harmelin Y, Boukari F, et al. (2014). Differences in visible light-induced pigmentation according to wavelengths: A clinical and histological study in comparison with UVB exposure. Pigment Cell Melanoma Res;27:822-6.
103. Kohli I, Chaowattanapanit S, Mohammad TF, Nicholson CL, Fatima S, Jacobsen G, et al. Synergistic effects of long-wavelength ultraviolet A1 and visible light on pigmentation and erythema. Br J Dermatol 2018;178:1173–80.
104. Bernerd F, Passeron T, Castiel I, Marionnet C. The Damaging Effects of Long UVA (UVA1) Rays: A Major Challenge to Preserve Skin Health and Integrity. Int J Mol Sci. 2022 Jul 26;23(15):8243.
105. Seçkin HY, Kalkan G, Baş Y, Akbaş A, Önder Y, Özyurt H, et al. Oxidative stress status in patients with melasma. CutanOculToxicol 2014;33(3):212-7.

Abbreviations

MELASQoL: Melasma Quality of Life
mMASI: Modified Melasma Area and Severity Index
GAIS: Global aesthetic improvement scale
EI: Erythema Index
MI: Melanin Index
TEWL: Trans epidermal water loss
p44/42 MAPK: p44/42 Mitogen activated protein kinase
PPAR-α (NR1C1) Peroxisome proliferator-activated receptor alpha (Nuclear receptor sub family 1, group C, member 1 protein)
L-DOPA: Levodopa (l-3, 4- dihydroxyphenylalanine)
COL 1A: Collagen type I alpha 1 chain
COL 3A: Collagen type III alpha 1 chain
ALOX15B: Arachidonate 15-lipoxygenase type B

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