ISSN: 2755-984X

Journal of Tumor Science Research

SCIENTIFIC Research and Community

Review Article

Open Access

Management of Melasma: Emerging Facts

Rabin Jung Thapa, Bal Chandra Karki and Satish Chandra Yadav*

Chongqing Medical University, Chongqing, China

ABSTRACT

Melasma is a dark or tan discoloration of the skin, whose exact cause is still unclear however sun exposure, hormonal influences, phototoxic drugs, and genetic factors are some of attributing factors. It is more common in females; with an 80% distribution is Centro-facial. Pathophysiologically, melasma shows the surge in dermal and epidermal pigmentation along with melanosomes, perivascular lymphohistiocytic infiltrates, and expansion of melanocytes. The latest treatment regimens include oral, topical, and procedural therapies. Conventional treatment of melasma includes hydroquinone, tretinoin, corticosteroids, and triple combination creams; Tranexamic acid, Polypodium leucotomos, and glutathione are newer drugs that have shown propitious effects. Techniques such as chemical peels, micro-needling, radiofrequency, and laser are also widely used as first-line or complementary treatments for melasma. Combing different treatment modalities have shown better efficacy than monotherapy. The objective of this review is to update the current emerging treatment modalities of melasma.

***Corresponding author**

Dr. Satish Chandra Yadav, MBBS, MD, Chongqing Medical University, Chongqing, China. E-mail: superior_satish@yahoo.com

Received: July 13, 2022; **Accepted:** August 24, 2022; **Published:** August 31, 2022

Keywords: Melasma, Pigmentation, Triple Combination Creams, Laser

List of Abbreviations
AzA: Azelaic Acid
HQ: Hydroquinone
IPL: Intense Pulsed Light
KA: Kojic acid
MASI: Melasma Area and Severity Index
NAFL: Nonablative Fractional Laser
GSH: Glutathione
Nd:YAG: Neodymium-Doped Yttrium Aluminum Garnet
PIH: Post-inflammatory hyperpigmentation
PIPA: Post-Inflammatory Pigment Alteration
QSRL: Q-switched ruby laser
RF: Monopolar radiofrequency
ROS: Reactive Oxygen Species

Introduction

Melasma is a word that came from a Greek root, Melas means black. Melasma (also called chloasma faciei) is a dark or tan discoloration of the skin [1]. The exact cause of melasma is still unclear however some attributing factors are sun exposure, hormonal influences, phototoxic drugs, and genetic factors [2]. This disorder is more common in female especially pregnant women (also known as the mask of pregnancy) and those taking pills and hormonal therapy [3]. Clinically, Melasma is hyper-melanosis generally present in symmetric patterns: The most common pattern is Centro-facial up to 80% of patients have pigmentation on the forehead, nose, and upper lip, excluding the philtrum, cheeks, and chin [4, 5]. The malar and mandibular lesions are seen on the cheeks, nose, and ramus of the mandible respectively are less common. Extra-facial melasma is a newer pattern commonly seen on the neck, sternum, forearms, and upper extremities [6]. The treatment of melasma is very challenging, due lack of clear pathophysiology. However, the latest regimens that include oral, topical, and procedural therapies are a revolution in the field of melasma treatment.

Epidemiology of Melasma

The exact prevalence of melasma is still unknown, due to variation among geographic locations and ethnic groups. However, most studies reported that the prevalence of melasma varies from 1 to 50% among the general population to high-risk populations [7-10]. The most common age of onset is 20-30 years, but mandibular types are seen in the patients in their 40s [5, 11, 12].

Melasma is most common in women than in men in the 9:1 ratio: however, a study from Brazil and India found the ratio 39:1 and 4:1 respectively [11, 13]. The prevalence of melasma among pregnant women ranges between 15 and 50 percent [7, 8]. The global prevalence of melasma varies in different locations 8.8% in Latino women, 2.9% in Saudi women, and 1.5% in Ethiopian women [9, 14, 15]. The causes of Melasma are multi-factorial. However, UV light plays an important role in triggering and exacerbating melasma. UV light produces reactive oxygen through nitric oxide activation resulting in melanogenesis. A recent study found that visible light of 415nm wavelength can cause enlarged pigmentation that could last for 3 months. Pathophysiologically, melasma shows the surge in dermal and epidermal pigmentation along with melanosomes, perivascular lymphohistiocytic infiltrates, and expansion of melanocytes.

Treatment

The treatment of melasma is arduous, due to inadequate responses and multiple relapses. The best clinical effects are achieved by

combining therapy that targets various pathologic aspects, such as photo-damage, inflammation, distorted vascularity, and unusual pigmentation. The combination therapy includes topical, oral, and procedural techniques, which limit melanin synthesis, epidermal turnover, and remove melanin without influencing its biosynthesis or melanosome transfer from melanocytes to keratinocytes [16-18].

The management of melasma typically starts with the elimination of risk factors, strict ultraviolet sun protection, and topical lightening formulations (such as botanical, corticosteroids, retinoid, and hypo pigmenting agents). These treatments may temporarily improve the skin condition but the pigmentation often returns, therefore the main goal includes the inhibition of pathways that synthesize melanin, a decrease of melanosome transfer from melanocytes to keratinocytes, and acceleration of pathways to remove melanin. The proposed therapeutic ladder for Melasma management is shown in (Table 1).

Table 1: Steps in Management of Melasma

First-line Treatment
➢ Control of risk factors (sun protection, discontinue hormone treatments or photosensitizing medications) ➢ Topical anti-Tyrosinase therapy - Other inhibitors of the melanin synthetic pathway (e.g., protease-activated receptor-2 inhibitor) - Topical exfoliant ➢ Triple combination topical cream, if tolerate.
⇩
Second-line Treatment
Combination of first-line treatments + series chemical peels.
⇩
Third-line Treatment
Combination of first-line treatments with: ❖ NAFL (1927 nm) ❖ NAFL (1550 nm, 1540 nm, or 1440 nm)
⇩
Fourth-line Treatment
Combination of first line treatments with: o Intense pulsed light (test spots) o Q-switch laser ractional radiofrequency devices

Topical Treatment

Topical applications are the first-line treatments for melasma. Targets of topical agents are to disrupt the enzymatic processes of pigments production. In many cases, topical agents are used according to the states of disease but the condition, more often than not, relapses [19]. Topical agents are frequently used in combinations with other treatments such as chemical peels, lasers, and intense pulse light sources. Since it is a long-term treatment plan, it is wise to take a detailed history of oral contraceptives or any phototoxic, anti-seizure medications and the usage of cosmetics. The patient should avoid the use of scented cosmetics and oral pills. Topical agents are exceedingly beneficial in the epidermal type of melasma [20].

Hydroquinone (HQ)

Hydroquinone (HQ), also known as dihydroxybenzene is an aromatic organic compound of phenol type; which decreases the formation of melanin in the skin. Melanin is the pigment that gives brown color to the skin. Hydroxyphenolic compounds are structurally similar to precursors of melanin. Dihydric phenol inhibits the conversion of DOPA to melanin by the tyrosinase enzyme, which results in the prevention of melanin synthesis [21]. The formation, melanization, and degradation of melanosomes are affected by hydroquinone (HQ). It further affects the structures of melanocytes which cause necrosis [22].

HQ is chiefly used to treat depigmentation. It has remained the gold standard for the treatment of melasma. For melasma treatment, (2-4)% concentration of HQ preparations are used once daily. Effects are noticeable after 5 to 7 weeks; however, treatment should be continued for three months to one year at least. HQ is often used with other combinations like glycolic acids, topical steroids, retinoids, and sunscreens [20]. HQ combines with Kligman's formula, Modifilide Kligman's, Westerhof's formula, and Pathak's formula. Kligman's formula (5% HQ, 0.1% tretinoin and 0.1% dexamethasone). Modified Kligman's (4% HQ, 0.05% tretinoin, and 1% hydrocortisone acetate). Westerhof's formula (4.7% N-acetylcysteine, 2% HQ and 0.1 triamcinolone acetonide) [23].

The adverse reactions of HQ are related to its dose and treatment durations. The major complication is skin irritation while mild burning, redness (erythema) stinging, dryness, allergic contact dermatitis, nail discoloration, transient hypochromia, and paradoxical post-inflammatory hypermelanosis are also seen [23].

Azelaic Acid (AzA)

The exact mechanism of action of azelaic acid is unspecified. However, in a vitro study it has been observed that, it inhibits nine carbon dicarboxylic acid of tyrosinase, resulting in antiproliferative and cytotoxic effects [17, 24]. Studies have also shown that 20% azelaic acid cream is as effective as 4% Hcqs cream but more effective than 2% Hcqs cream alone [25, 26]. It takes 1-2 months to produce skin lightening effects [20]. The adverse effects of Azelaic Acid are Pruritus, tingling, stinging, mild erythema, peeling and burning [27].

Kojic Acid (KA)

Kojic acid is a 5-hydroxy-2-hydroxymethyl-4-pyrone, which is a chelating agent and has an anti-oxidant effect. Kojic Acid inhibits tyrosinase by chelating copper at the enzyme's active site. It is derived from fungi namely Acetobacter, Aspergillus, and Penicillium. 2% Kojic acid cream widely used in Asia, however less effective than Hcqs and causes skin Irritation and sensitization [28-31].

Tretinoin

Tretinoin is the carboxylic acid form of vitamin A, also known as all-trans retinoic acid (RA). Tretinoin improves pigmentation by inhibiting several steps in the melanization pathway. Retinoids, such as tretinoin, vitamin A and retinoic acid (RA) were first used in combination with HQ. Later penetration introduces its effect on melanogenesis [32, 33]. Tretinoin assists in the rapid loss of pigment through epidermopoiesis and increased epidermal turnover also decrease the contact time between keratinocytes and melanocytes. Additionally, there is evidence to inhibit the induction of tryosinase melanogenesis and DOPA chrome conversion factors [34]. Clinically significant skin lightning becomes evident only after 24 weeks. Tretinoin can also be used as a peeling mask. Tretinoin has a good therapeutic response but better results are obtained in combination with agents like HQ and corticosteroids [35]. The most common side effect of tretinoin is erythema, a retinoid dermatitis characterized by burning, stinging, dryness, and scaling. Tretinoin can be irritating must adjust to prevent inflammation. Inflammation can cause hyperpigmentation, predominantly in people with dark skin [33, 36]. It is better to use sunscreens during treatment with retinoic acid to avoid its side effects.

Corticosteroids

Corticosteroids are hormones that are produced in the adrenal cortex of vertebrates, but synthetic analog are also available. Corticosteroids are of two types: One is glucocorticosteroids another one is mineral corticosteroids. Pigmentation can be prevented by non-selective suppression of melanogenesis with anti-inflammatory effects [37]. Corticosteroid inhibits the synthesis of melanin, and its mediators like prostaglandin and leukotriene, which result in skin lightening. Therapeutic responses are good, however less effective than other depigmenting agents when used alone [38]. Topical steroids can be used solely, however, long-term benefits are fewer and more side effects: rosacea-like dermatosis (erythema, Pustules, and papules on Centro facial area), dermatitis, hypertrichosis, epidermal atrophy, steroid-induced acne, and telangiectasia are seen.

Oral Treatment of Melasma

Most commonly used oral therapies for Melasma management are Tranexamic Acid (TA), Polypodium Leucotomos and Glutathone.

Tranexamic Acid (TA)

The hemostatic agent, Tranexamic acid, is a synthetic derivative of lysine; It inhibits the binding of plasminogen to the receptor expressed by keratinocytes, which results in the reduction of UV-induced plasmin activity, tyrosinase activity, prostaglandin production as well as melanocyte-stimulating hormone levels [39, 40]. It also inhibits angiogenesis, a contributing factor of melasma by reducing vascular endothelial growth factor (VEGF) and endothelin-1, chemical signals [28, 41, 42]. The oral dose of Tranexamic acid is 250mg two times daily as adjunctive therapy in patients who do not have an effective result with Hcqs or triple therapy cream [43]. The common side effects of Tranexamic acid are pale skin, headache, tinnitus, abdominal bloating, irregularities of the menstrual cycle, mild gastrointestinal discomfort, allergic skin rashes, alopecia, and deep venous thrombosis (DVT) [44].

Polypodium Leucotomos

Polypodium leucotomos is a fern found in south and central America, is currently used as an oral medication for the treatment of melasma [39, 45-47]. It inhibits cyclooxygenase-2 triggered by UV radiation and promotes expression of the p53 suppressor gene, modulation of inflammatory cytokines, and upregulation of endogenous antioxidant systems [48]. When used with hydroquinone, P. leucotomos extract may expedite clinical improvements. A study carried out in 33 Asian women showed that 12 weeks treatment with topical Hcqs 4%, sunscreen SPF 50+ and oral P. leucotomos extract; 75% improvement in MASI scores [49]. The recommended dose of P. leucotomos extract is 480-1200mg daily, with no major side effects.

Glutathione (GSH)

Glutathione is an endogenous anti-oxidant that consists of three amino acids namely glutamine, cysteine, and glycine. It prevents cellular damage caused by reactive oxygen; inhibits tyrosinase to reduce inflammation, and produces skin whitening effects due to an increase in pheomelanin ratio compared to eumelanin [28]. A study in 2016, showed that 500 mg glutathione lozenge taken once daily for eight weeks has a significant decrease in melanin level [50]. A similar study was carried out in 2014, where 2% glutathione lotion was used twice daily for 10 weeks, which showed 67% skin whitening [51]. No major side effects were seen with lozenge or lotions.

Chemical Peels

Chemical peels have been frequently used in the treatment of melasma as they can increase epidermal remodeling and keratinocyte turnover. The most commonly used peels are glycolic acid (GA). A study in 2016 found that a combination of 20 percentage Salicylic acid and 10 percentage mandelic acid are as effective as 35 percent glycolic acid over 12 weeks of treatment [52]. Another chemical peels Trichloroacetic acid, 10-20 percent of TA has the same effect as GA peels however it has more side effects like burning and peeling [53].

Micro Needling

Microneedling or mesotherapy is a process to distribute a small number of topical drugs intra-dermally by making tiny channels in the skin [54]. It also helps in the placement of drugs to the deeper epidermis and dermis; Also stimulates wound healing response [55, 56]. A study carried in 2011 showed that delivering topical drugs with micro needing significant improvement of MASI scores. The common side effects are Erythema, Tram track marks, and Post-inflammatory Pigment alteration.

Lasers and Light Therapies

LASER stands for light amplification by stimulated emission of radiation are devices that release electromagnetic radiation that can be used to ablate tissues. Recently, a laser has been commonly used for the treatment of melasma. It is based on the principle of selective photothermolysis that selectively targets chromophores cells. The wavelength and duration of light are short, that are easily absorbed by chromophores cells, which result in selective heating and thermal injury to the pigmented tissues [57-59]. The various wavelengths of laser penetrate varying depths, which help clinicians to target various depths in melasma.

Nonablative fractional lasers –It has the slowest chance of recurrence after treatment while quality-switched (QS) lasers have a rapid recurrence rate. The wavelength of 1927 nm is effective against epidermal pigmentation, and wavelengths of 1440, 1540, and 1550 nm are effective against dermal melasma. Quality-switched neodymium-doped yttrium aluminum garnet (QS-Nd: YAG) – The wavelength of 1064 nm is effective against the melasma, as it damages the upper dermal vascular plexus and help in collagen formation. Despite the rapid relapse, QS-Nd: YAG laser is most commonly used [18, 60].

Pulsed dye laser (PDL) –It is very useful for vascular lesions as angiogenesis contributes to melasma formation [41, 42 ,61, 62]. Intense pulsed light (IPL) –It emits light of 500 to 1200 nm wavelength which helps the clinician to modulate wavelength, the duration for accurate targeting of melasma cells resulting in thermolysis [60]. A study conducted in 2010, found that IPL use in hyperpigmented areas and dark tones have excellent results in 47% while 29% good and 13% has moderate results [63]. Since IPL targets all layers of skin, it can damage normal skin, thus not recommended for darker tones (Fitzpatrick skin types IV through VI).

A study carried out in 2010, among 22 Asian patients who were treated with 2% hydroquinone alone or a combination of laser with hydroquinone 2%, the result showed that the MASI score and colorimetric relative lightness score improved by 76% and 93% in combined treatment while 24% and 20% improvement in hydroquinone alone side [64]. In 2018, A Korean doctor treated 40 patients with a QS-Nd: YAG laser for 10 weeks, study showed a 54% improvement in MASI scores after 10 weeks, 30 patients had better improvement while 4 patients had no improvement post-laser [65]. A similar study was carried out by Kauvar AN in 27 patients, who were treated with the combination of microdermabrasion followed immediately by QS-Nd: YAG over 4 weeks. 50% showed improvement within a month, while 95% clearance was seen in 40% of patients over 3 to 12 months. Side effects: Melasma pigmentation may get worse or streaked hypopigmentation may be seen post-laser treatment. It is wise to use sunscreen post-laser.

Melasma treatments, Mechanisms of Action, and Adverse Effects are shown in Table 2. The treatment of melasma is still challenging due to unclear causes and multiple relapses post-treatment. Among the current topical treatment, Hydroquinone is the gold standard. Nowadays hydroquinone, retinoic acid, and corticosteroids are the first-line treatment for this pigmentary disorder. Procedural treatments are famous in this era such as chemical peels, IPL, micro-needling, and laser. Still, we need more research about melasma, for better understanding of the causes and treatment.

Table 2: Medicines,MOA and its effects

Modality	Drugs	Mode of action	Side effects
Topical	Hydroquinone (HQ),	✓ Tyrosinase inhibitor. ✓ Melanocytes DNA and RNA synthesis inhibition	Irritation, exogenous ochronosis (with HQ)
	Azelaic acid,	o Tyrosinase inhibition o Melanocyte proliferation inihibation	Irritation, erythema, Pruritis
	Kojic acid	• Tyrosinase inhibition • ROS scavenger	Irritation, sensitization
	Tretinoin	Increased keratinocyte turnover	Irritation, redness
	Corticosteroids	Anti-inflammatory with non-selective inhibition of melanogenesis	Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation
oral	Tranexamic acid	Inhibits plasminogen/plasmin pathway → inhibition of melanin synthesis Decreases vascular proliferation	Abdominal bloating, menstrual irregularities, headache, deep venous thrombosis
	a.Polypodium leucotomos b.Glutathione	Inhibition of reactive oxygen species	No significant AE
Procedural	Q-switch ruby laser, Q-switch Nd:Yag laser	Melanosome destruction	Burn, post inflammatory pigment alteration (PIPA)
	Non-ablative fractional lasers.	Fractional photothermolysis leading to melanin extrusion.	Burn,PIPA
	Chemical peels	Increased keratinocyte turnover	Burn, peeling, PIPA
	Microneedlings	Transdermal drug delivery.	Erythema, edema, tram-track marks, PIPA
	Intensepulsed light	Extrusion of melanosomes	Burn, PIPA
	Radiofrequency	Cellular biostimulation Transdermal drug delivery	Burn

Source: Oluwatobi A. Ogbechie-Godec . Nada Elbuluk ; Dermatol Ther (Heidelb) (2017) 7:305–318

Disclosures

Conflict of Interest: There is no conflict of interest to declare.

Financial Ties: None.

References

1. James William, Berger Timothy, Elston Dirk (2005) Andrews' Diseases of the Skin: Clinical Dermatology. (10th ed.). Saunders. ISBN 0-7216-2921-0.
2. Melasma |American Academy of Dermatology. www.aad.org. Retrieved 2016-02-25.
3. Tunzi M, Gray GR (2007) Common skin conditions during pregnancy. Am Fam Physician 75: 211-18.
4. Guinot C, Cheffai S, Latreille J, Dhaoui MA, Youssef S, et al. (2010) Aggravating factors for melasma: a prospective study in 197 Tunisian patients. J Eur Acad Dermatol Venereol 24: 1060-1069.
5. Tamega Ade A, Miot LD, Bonfietti C, Gige TC, Marques ME, et al. (2013) Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. J Eur Acad Dermatol Venereol 27: 151-156.
6. Ritter CG, Fiss DV, Borges da Costa JA, de Carvalho RR, Bauermann G, et al. (2013) Extra-facial melasma: clinical, histopathological, and immunohistochemical case–control study. J Eur Acad Dermatol Venereol 27: 1088-1094.
7. Moin A, Jabery Z, Fallah N (2006) Prevalence and awareness of melasma during pregnancy. Int J Dermatol 45: 285-288.
8. Rathore SP, Gupta S, Gupta V (2011) Pattern and prevalence of physiological cutaneous changes in pregnancy: a study of 2000 antenatal women. Indian J Dermatol Venereol Leprol 77: 402.
9. Werlinger KD, Guevara IL, Gonzalez CM, Rincon ET, Caetano R, et al. (2007) Prevalence of self-diagnosed melasma among premenopausal Latino women in Dallas and Fort Worth, Tex. Arch Dermatol 143: 424-425.
10. Taylor SC (2003) Epidemiology of skin diseases in ethnic populations. Dermatol Clin 21: 601-607.
11. Achar A, Rathi SK (2011) Melasma: a clinico-epidemiological study of 312 cases. Indian J Dermatol 56: 380-382.
12. Mandry Pagan R, Sanchez JL (2000) Mandibular melasma. P R Health Sci J 19: 231-234.
13. Hexsel D, Lacerda DA, Cavalcante AS, Machado Filho CA, Kalil CL, et al. (2014) Epidemiology of melasma in Brazilian patients: a multicenter study. Int J Dermatol 53: 440-444.
14. Parthasaradhi A, Al Gufai AF (1998) The pattern of skin diseases in Hail Region, Saudi Arabia. Ann Saudi Med 18: 558-561.
15. Hiletework M (1998) Skin diseases seen in Kazanchis health center. Ethiop Med J 36: 245-254.
16. Sardana K, Ghunawat S (2015) Rationale of using hypopigmenting drugs and their clinical application in melasma. Expert Rev Clin Pharmacol 8: 123.
17. Ball Arefiev KL, Hantash BM (2012) Advances in the treatment of melasma: a review of the recent literature. Dermatol Surg 38: 971.
18. Trivedi MK, Yang FC, Cho BK (2017) A review of laser and light therapy in melasma. Int J Womens Dermatol 3: 11.
19. Rigopoulos D, Gregoriou S, Katsambas A (2007) Hyperpigmentation a single and melisma. J Journal of Cosmetic Dermatology 6: 195-202.
20. Prignano F, Ortonne JP, Buggiani G, Lotti T (2007) Therapeutic approaches to melisma. J Dermatology Clinics 25: 337-342.
21. Palumbo A, d'ischia M, Misuraca G, Prota G (1998) Mechanism of inhibition of melanogenesis by hydroquionone disorders. J International Journal of Dermatology 37: 449-450.
22. Jimbow K, Obata H, Pathak MA, Fitzpatrick TB (1974) Mechanism of depigmentation by hydroquinone. J Journal of Investigative Dermatology 62: 436-449.
23. Cestari TF, Hexsel D, Viegas ML, Azulay L, Hassun K, et al. (2006) Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: the MelasQoL-BP study and improvement of QoL of melasma patients after triple combination therapy. J British Journal of Dermatology 156: 13-20.
24. Farshi S (2011) Comparative study of therapeutic effects of 20% azelaic acid and hydroquinone 4% cream in the treatment of melasma. J Cosmet Dermatol 10: 282.
25. Baliña LM, Graupe K (1991) The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. Int J Dermatol 30: 893.
26. Verallo-Rowell VM, Verallo V, Graupe K (1989) Double-blind comparison of azelaic acid and hydroquinone in the treatment of melasma. Acta Derm Venereol Suppl (Stockh) 143: 58.
27. Grimes PE (2009) Management of hyperpigmentation in darker racial ethnic groups. Semin Cutan Med Surg 28: 77.
28. Ogbechie-Godec OA, Elbuluk N (2017) Melasma: An Up-to-Date Comprehensive Review. Dermatol Ther (Heidelb) 7: 305.
29. Cestari T, Arellano I, Hexsel D (2009) Melasma in Latin America: options for therapy and treatment algorithm. J Eur Acad Dermatol Venereol 23: 760.
30. Shankar K, Godse K, Aurangabadkar S (2014) Evidence-based treatment for melasma: expert opinion and a review. Dermatol Ther (Heidelb) 4: 165.
31. Kindred C, Okereke U, Callender V (2013) Skin-lightening agents: An overview of prescription, office-dispensed, and over-the-counter products. Cosmetic Dermatology 18.
32. Halder R, Noruld JJ (1998) Topical tretement of pigmentary disorders. In: Nordloud JJ, Boissy RE, Hearing VJ, King RA, orronene JP, editors. The pigmentary system physiology and pathology New York. J Oxford university Press 969-975.
33. Gupta PAK, Gover MD, Nouri K, Taylor S (2006) The treatment of melasma: A review of clinical trials. J Journal of the American Academy Dermatology 55: 1048-1065.
34. Kligman AM, Willis I (1975) A new formula for depigmenting human skin. J Archives of Dermatology 111: 40-48.
35. Dogra S, Kanwar AJ, Parsad D (2002) Adapalene in the treatment of melasma: A preliminary report. J Journal of Dermatology 29: 539-540.
36. Murray L (2003) Physicians desk refrence. 57th ed. Montvale, NJ. J Thomson PDR 545, 945, 1387.
37. Deo KS, Dash KN, Sharma YK, Virmani NC, Oberai C (2013) Kojic acid vis-a-vis its combinations with hydroquinone and betamethasone valerate in melasma: a randomized, single blind, comparative study of efficacy and safety. J Indian Journal of Dermatology 58: 281-285.
38. Neering H (1975) Treatment of melasma (chloasma) by local application of a steroid cream. J Dermatology 151: 349-353.
39. Grimes PE (1995) Melasma. Etiologic and therapeutic considerations. Arch Dermatol 131: 1453.
40. Lee JH, Park JG, Lim SH, Kim JY, Ahn KY, et al. (2006) Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. Dermatol Surg 32: 626.
41. Kwon SH, Hwang YJ, Lee SK, Park KC (2016) Heterogeneous Pathology of Melasma and Its Clinical Implications. Int J Mol Sci 17.
42. Kim EH, Kim YC, Lee ES, Kang HY (2007) The vascular

characteristics of melasma. J Dermatol Sci 46: 111.
43. Wang JV, Jhawar N, Saedi N (2019) Tranexamic Acid for Melasma: Evaluating the Various Formulations. J Clin Aesthet Dermatol 12: E73.
44. Lee HC, Thng TG, Goh CL (2016) Oral tranexamic acid (TA) in the treatment of melasma: a retrospective analysis [J]. Journal of American Academy of Dermatology 75: 385-392.
45. Nestor M, Bucay V, Callender V, Cohen JL, Sadick N, et al. (2014) Polypodium leucotomos as an Adjunct Treatment of Pigmentary Disorders. J Clin Aesthet Dermatol 7: 13.
46. Ahmed AM, Lopez I, Perese F, Vasquez R, Hynan LS, et al. (2013) A randomized, double-blinded, placebo-controlled trial of oral Polypodium leucotomos extract as an adjunct to sunscreen in the treatment of melasma. JAMA Dermatol 149: 981.
47. Kohli I, Shafi R, Isedeh P, Vasquez R, Hynan LS, et al. (2017) The impact of oral Polypodium leucotomos extract on ultraviolet B response: A human clinical study. J Am Acad Dermatol 77: 33.
48. Grimes PE, Ijaz S, Nashawati R, Kwak D (2019) New oral and topical approaches for the treatment of melasma. Int J Womens Dermatol 5: 30.
49. Goh CL, Chuah SY, Tien S, Thng G, Vitale MA, et al. (2018) 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 11: 14.
50. Handog EB, Datuin MS, Singzon IA (2016) An open-label, single-arm trial of the safety and efficacy of a novel preparation of glutathione as a skin-lightening agent in Filipino women. Int J Dermatol 55:153.
51. Watanabe F, Hashizume E, Chan GP, Kamimura A (2014) Skin-whitening and skin-condition-improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women. Clin Cosmet Investig Dermatol 7: 267.
52. Sarkar R, Garg V, Bansal S, Sethi S, Gupta C (2016) Comparative evaluation of efficacy and tolerability of glycolic acid, salicylic mandelic acid, and phytic acid combination peels in melasma. Dermatol Surg 42: 384-391.
53. Kumari R, Thappa DM (2010) Comparative study of trichloroacetic acid versus glycolic acid chemical peels in the treatment of melasma. Indian J Dermatol Venereol Leprol 76: 447.
54. Fabbrocini G, De Vita V, Fardella N, Pastore F, Annunziata MC, et al. (2011) Skin needling to enhance depigmenting serum penetration in the treatment of melasma. Plastic Surg Int 158241.
55. Budamakuntla L, Loganathan E, Suresh DH, Shanmugam S, Suryanarayan S, et al. (2013) A randomised, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with melasma. J Cutan Aesthet Surg 6: 139-143.
56. Hou A, Cohen B, Haimovic A, Elbuluk N (2017) Microneedling: a comprehensive review. Dermatol Surg 43: 321-339.
57. Attwa E, Khater M, Assaf M, Haleem MA (2015) Melasma treatment using an erbium: YAG laser: a clinical, immunohistochemical, and ultrastructural study. Int J Dermatol 54: 235.
58. Goldberg DJ (1997) Laser treatment of pigmented lesions. Dermatol Clin 15: 397.
59. Anderson RR, Margolis RJ, Watenabe S, Flotte T, Hruza GJ, et al. (1989) Selective photothermolysis of cutaneous pigmentation by Q-switched Nd: YAG laser pulses at 1064, 532, and 355 nm. J Invest Dermatol 93: 28.
60. Arora P, Sarkar R, Garg VK, Arya L (2012) Lasers for treatment of melasma and post-inflammatory hyperpigmentation. J Cutan Aesthet Surg 5: 93.
61. Passeron T (2013) Long-lasting effect of vascular targeted therapy of melasma. J Am Acad Dermatol 69: e141.
62. Li JY, Geddes ER, Robinson DM, Friedman PM (2016) A review of melasma treatment focusing on laser and light devices. Semin Cutan Med Surg 35: 223.
63. Zoccali G, Piccolo D, Allegra P, Giuliani M (2010) Melasma treated with intense pulsed light. Aesthetic Plast Surg 34: 486.
64. Wattanakrai P, Mornchan R, Eimpunth S (2010) Low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser for the treatment of facial melasma in Asians. Dermatol Surg 36: 76.
65. Choi JE, Lee DW, Seo SH, Ahn HH, Kye YC (2018) Low-fluence Q-switched Nd:YAG laser for the treatment of melasma in Asian patients. J Cosmet Dermatol 17: 1053.