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REVIEW ARTICLE

Tranexamic acid, A Promising Melasma Treatment Modality; Past and Future Treatment Regimen

[(1)] Amany Abdel Rahman Nassar, [(1)] Khaled Mohamed Gharib, [(1)] Basma M. Abdel-Azim, [(2)] Mohamed A. Akl.
[(1)] Dermatology, Venereology and Andrology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[(2)] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo, Egypt

***Corresponding Author:**
Mohamed A. Akl
E-mail:mohamedakl@azhar.edu.eg

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ABSTRACT

Melasma is a chronic recurrent, acquired hyper-melanosis that arises exclusively in sun-exposed areas. With a high recurrence rate, melasma presents a great therapeutic challenge. Conventionally, the cornerstones of melasma therapies have been topical whitening agents and stringent photoprotection. Chemical peels, dermabrasion, and laser treatments are other adjuvant treatment modalities that have shown limited efficacy. There has recently been a growing interest in investigating the impacts of tranexamic acid (TA) on melasma and has shown promise. TA has been investigated for melasma treatment in a variety of formulas, which include topical, intradermal (ID), and oral administration, with oral formulations showing the highest albeit transient benefit. Topical therapy is often recommended over systemic therapy for hyperpigmentation disorder because it delivers medicine directly to the diseased area, leading to fewer side effects and improved patient compliance. Throughout this brief review, we explain the various regimens of TA for melasma, as well as other suggested research directions with an emphasis on nanotechnology that should be pursued in the future.

Key words: Melasma, Skincare; Tranexamic acid; lipid-based nanovesicles; Chitosan nanoparticles.

INTRODUCTION

Melasma (chloasma or pregnancy mask) is acquired hyper-melanosis that affects persons of Asiatic (Asian), Africans, and Spanish origin disproportionately. Melasma is distinguished by the darkening of solar-exposed face skin, particularly the cheeks, forehead, chin, upper lip, and supralabial areas **[1]**. Melasma is more commonly seen in females than in males with prevalence of ~ 40% and 20%, respectively **[2]**.

The pathogenesis of melasma is still unclear, however ultraviolet (UV) radiation often combined with genetic, and hormonal factors are the major melasma-related pathological factors **[3]**. Melasma is classified into four histological kinds based on Wood's lamp and the level of pigmentation accumulation: epidermal, dermal, mixed, and telangiectatic melasma **[4]**.

In spite of various treatment arms, melasma is still challenging. Different treatment modalities such as topical therapy, systemic therapy and various procedural therapeutic options have been utilized in different studies with varying but less satisfactory outcomes **[5]**. Conventionally, the cornerstones of melasma therapy have been topical whitening treatments and stringent UV protection. Exfoliating, dermabrasion, and laser therapy are other adjunct therapeutic techniques that have shown minimal success **[6]**.

Although Kligman formula composed of hydroquinone 5%, tretinoin 0.1% and 1 % hydrocortisone, is the corner stone of treatment of epidermal melasma **[7]**. There has recently been a surge of interest in researching the benefits of TA on melasma therapy.

TA lysine-derived synthesized amino acid. It has been hypothesized that TA is a fibrinolytic agent with antiplasmin properties that has the ability to prevent the production of paracrine melanogenic substances, which ordinarily promote melanocytes **[8]**. As a skin-lightening agent, TA has been studied

in a variety of formulations for the treatment of melasma, including topical, ID, as well as oral **[6]**.
However, TA's significant potential for melasma treatment is hindered by its poor skin permeation and deposition. For the following reasons, TA, a hydrophilic molecule, is ineffective for topical administration into melanocytes in the epidermal basal layer: (i) TA has a difficult time passing through the stratum corneum's lipid barriers; (ii) TA is poorly maintained in the epidermis's basal layer, making it difficult for it to reach melanocytes **[9]**.
Numerous approaches have been made to ameliorate the skin permeation of topical TA by loading in nano and microscale system. Drug delivery via phospholipid (PL)- based vesicular systems has sparked interest for both topical and dermal drug delivery. Vesicles, in particular, are thought to be capable of breaching the stratum corneum (SC) barrier in intact skin, resulting in the efficient delivery of drug molecules **[10]**.
Transfersomes® are main deformable, elastic PL-based-vesicles invented in the 1990s by Cevc et al. Transfersomes® are made up of PL and edge activators like Tween or Na-cholate, which results in elastic carriers for enhanced topical medication delivery. The promising results obtained with Transfersomes® prompted the creation of additional innovative flexible vesicles via vesicular composition changes. Early studies have shown that elastic vesicles such as ethosomes [have a higher percentage of ethanol (ETOH)] [**11]** have potential as drug carriers. Invasomes are innovative flexible PL vesicles that contain a combination of soy phosphatidylcholine (PC), terpenes, and ETOH that penetrate the skin better than liposomes **[10]**.
In the same way, Chitosan based nanocarrier is a biodegradable, biocompatible cationic polymer having minimal toxicity, and high bioadhesive qualities, which are very promising for drug delivering (as TA) to the dermis layer via barriers of the SC **[12]**.
Even though published research has been backed up the effectiveness and safety of TA **[6]**, there is still a scarcity of adequately powered medical trials. There is currently no definite agreement on using of TA for melasma, indicating the necessity of vast, randomized control studies.

MELASMA

The term "melasma" comes from "melas" a Greek term meaning "black colour" The illness is sometimes referred to as "chloasma," which is a Greek phrase that meaning "green in colour" or "pregnancy face". It is distinguished medically by semi-symmetric light brown to bluish-gray macules and patches with irregular, sharp borders. Guttate, linear, or confluent pigmentation is possible **[13]**.
Melasma has been thought to be a harmless condition with only aesthetic implications; however, it might impact self-image and self-esteem, lowering the person's quality of life **[13]**. This ailment reduces people's quality of life by compromising their emotional and psychological well-being, and frequently drives patients to seek treatment from a dermatologist. People frequently express sense of guilt, poor self-esteem, discontent, and a lack of enthusiasm to engage in social activities. Suicidal thoughts have also been described in the literature **[14]**.

Epidemiology

Females are far more likely than males to suffer from the melasma. Although the overall prevalence of this condition in the population is unknown, one simple survey suggests that melasma may affect up to 40% of females and 20% of males. Melasma prevalence has also varied globally **[2]**. Positive family history was found in epidemiological studies, 36.3-48% of cases are familial.

Causes of melasma

The pathogenesis is not fully explained; nonetheless the main factor is UV sun light exposure **[3]**. Also, various pathological factors have been involved in melasma etiology, as genetic influences, racial, hormonal therapy, pregnancy, and contraceptive pills **[15]**.

Genetics and Racial Variables

Fitzpatrick skin type III Latin Americans, Hispanics, and Asians are predisposed to pigmentary condition, especially melasma and post-inflammatory hyperpigmentation (PIH). It highly impacts pigment skin phenotypes, as type III or IV in Singapore, type IV in Brazil, and skin type IV–VI in India **[16]**.

Sun Exposure

Many pathological theories have been proposed, including the effect of UV radiations on melanogenesis and melanosome transfer. It has an immediate effect on DNA. It also increases the expression of receptors for melanogenic factors on the cell surface. Other suggested that UV light rise plasmin activity in keratinocytes, resulted in an increase mast cells number that in-turn stimulates α-melanocyte stimulating hormone which increase melanogenesis, so increase melanin content and increase vascularization by vascular endothelial growth factor, which increase melanocyte proliferation and migration **[3]**.

Role of Hormones

Many cases report the worsening melasma onset during pregnancy, which is also known as "chloasma gravidarum" with onset typically occurring during the 2nd half of the gestational period. It, on the other hand, can appear before or after pregnancy **[17]**. Hormonal medications such as oestrogen, progesterone-containing contraceptive pills, di-ethyl-still-besterol, and finasteride (an anti-androgen) have been linked to an increase in melasma **[18]**.

Molecular pathogenesis

A total of 279 genes were stimulated in the study, with 152 found to be down-regulated, and many melanogenesis-related genes and melanocyte markers such as tyrosinase (TYR), microphthalmia-associated transcription factor (MITF), and TYRP1 found to be up-regulated **[19]**. Lipid metabolism is the most affected biological process in melasma. Peroxisome proliferator-activated receptor (PPAR) alpha, arachidonate 15-lipoxygenase type B (ALXO 15B), PPAR gamma coactivator 1 alpha, and diacylglycerol o-acyltransferase 2-like 3 were discovered to be down regulated; presumably down regulated by chronic UV exposure **[19]**.

other

(i) Cosmetic-induced facial hyperpigmentation may be poikiloderma of Civatte, the role of cosmetic ingredients (in synergy with UV exposure) in melasma causation cannot be ruled out. (ii) Phototoxic and photoallergic drugs, such as arsenic, iron, copper, bismuth, silver, and gold-containing medications, antiseizure drugs, and organic compounds such as quinacrine, have been linked to generalized hyperpigmentation and may play a role in the development of melasma **[20]**. (iii) Increased numbers of keratinocytes expressing Nerve growth factor receptor (NGFR) and hypertrophic nerve fibres in the superficial dermis of lesional skin indicate a neural component **[20]**.

Types of melasma

Based on Wood's lamp, and depending on the depth of pigment deposition, melasma is divided into four histological types: epidermal, dermal, mixed, and telangectatic type melasma **[7]**.

Epidermal melasma: the most common type of melasma, it is distinguished by an increase in melanin in the epidermal layers, intensify under Wood's light, and has a well-defined border, is dark brown in colour, and responds well to treatment.

Dermal melasma: has melanophages throughout the dermis and does not intensify under Wood's light. It has an ill-defined border, a light brown or bluish colour, and responds poorly to treatment.

Melasma of mixed type: this type of melasma has both epidermal and dermal pigmentation. It was made up of dark and light brown pigmented patches. It improves partially as a result of treatment.

Telangiectasias (vascular ecstasies or vascular stasis): are a permanent dilation of small blood vessels (capillaries, arterioles, and venules) that results in focal red lesions. It appears as non-pulsatile, fine, bright red lines or nets. Telangiectasias and melasma are both associated with elevated serum levels of melanocyte-stimulating hormone.

Melasma can also be classified based on its location: Centro-facial, includes the forehead, nose, upper lip, and chin. Malar includes the cheeks and nose. Mandibular, includes the mandibular ramus. Pattern on the lateral cheeks Extra-facial melisma has been reported in women who received exogenous progesterone in the upper arm, forearm, and shoulder.

Treatment

Like a chronic ailment with various contributing factors, the treatment of melasma remains a great challenge as there is no proven treatment modality and the primary goal is improving the pigmentation and self-esteem of patients. Different therapeutic approaches such as topical therapy, systemic therapy, and other auxiliary treatment techniques, like dermabrasion, laser therapy, and exfoliation have all shown minimal success **[6]**.

Topical treatment

Cosmetic Camouflage: Many patients consider camouflage makeup to be an important part of their melasma treatment **[20]**.

Hydroquinone (HQ): is a dihydric phenol, the gold standard of treatment for melasma. Many combinations have been used at a concentration of 2-4 %. It is inhibiting tyrosinase, the enzyme responsible for converting L-tyrosine to L-DOPA and the rate-limiting step in the melanin synthesis pathway **[21]**. Frequent adverse effects of HQ include irritation, erythema, stinging, irritating or allergic contact dermatitis, and temporary halo hypochromia in treated regions (which vary by dose and duration). The development of milia, paradoxical PIH, and exogenous ochronosis may be among the intermediate and long-term adverse effects of hydroquinone.

Azelaic acid (AZA 20%): it is act as HQ, but unlike HQ, AZA appears to primarily target overactive melanocytes, so it would not bleach skin with regularly functioning melanocytes. Skin

inflammation is the most significant adverse effect. It can be used during pregnancy **[22]**.

Tretinoin (0.01 to 0.1%): it acts via increase a keratinocyte turnover and a lower melanocyte activity. It also increases the permeability of the epidermis, permitting adjunct therapies to penetrate more effectively.

Kligman formula: it is composed of HQ 5%, tretinoin 0.1% and 1 % hydrocortisone, the corner stone of treatment of epidermal melasma **[7]**.

Silymarin: is a polypeptide flavonoid with antioxidant properties whose main component is silybin. It reduces the harmful effects of UV radiation and, in a dose-dependent manner, inhibits melanin production **[21]**.

Peeling (Exfoliating)

Exfoliating is a well-known treatment technique that is used as a 2nd option of melasma therapy and might be beneficial in improving its epidermal element. It can cause controlled epidermal dys-cohesion and subsequent regeneration and has superficial effects, such as allowing the elimination of epidermal pigment as well as melanin from keratinocytes and preventing melanosome migration to keratinocytes, making it an indispensable melasma management technique **[23]**.

Peels containing Alpha Hydroxy Acids (AHA), e.g., GA, mandelic acid and Beta Hydroxy Acids (BHA), e.g., salicylic acid (SA) and combined exfoliates such as Jessner's (resorcinol, SA and LA in ethanol) and Tretinoin peels are the important categories of peels being considered here. They begin with monthly treatments at the smallest formulation level (20%) and continue to weekly applications at greater concentrations **[23]**.

Laser

Lasers and light devices such as Q-switched lasers (QSL), fractional lasers, ablative lasers, and intense pulsing lights (IPLs) have shown disappointing results in the treatment of melasma. Furthermore, it is not recommended as single therapy in melasma management. Non-Ablative laser: several pigment lasers, including QSLs pulsed dye 510 nm lasers, QS ruby 694 nm lasers, QS alexandrite laser 755 nm lasers, and QS Nd **[24]**. Ablative lasers are accessible in a variety of wavelengths, such Er: YAG lasers at 2940 nm and CO2 lasers at 10600 nm [25]. Fractional lasers with transdermal drug delivery, such as the fractional QS Nd-Yag 1064nm and QS ruby 694 nm lasers, are available **[26]**.

Physical modalities

Microdermabrasion, alone or in conjunction with other treatment techniques, has been shown to be successful and well-tolerated therapy for hyperpigmentation. Only the stratum corneum is removed during microdermabrasion, leaving the epidermis intact. It has not yet been evaluated particularly for melasma management **[27]**.

TRANEXAMIC ACID

Recently, there has been an interest in studying the effects of tranexamic acid (TA) in melasma **[6]**. TA was reported for the first time in melasma treatment in Japan by Nijor in 1979 who found that that severity of melasma was significantly reduced after 2–3 weeks **[28]**.

TA mode of Action

The mode of action of TA in the reduction of melasma hyperpigmentation is not entirely understood but many theories have been suggested that TA serves as a plasmin inhibitor by reversibly blocking the lysine binding sites on the plasminogen molecule, thereby inhibiting the conversion of plasminogen to plasmin. TA also has antiplasmin activity and consequently inhibits melanin synthesis by block the active site of urokinase plasminogen activator (uPA) with high specificity (Ki = 2 mM) among all the serine proteases **[29]**. Other study suggested that TA inhibits melanin synthesis in melanocytes by interfering with the interaction of melanocytes and keratinocytes by inhibition of the plasminogen/ plasmin system. In addition, TA is like tyrosine in its structure, which means that it can competitively inhibit the enzymatic activity of tyrosinase **[8]**.

Route of TA Administration

TA has already been investigated for melasma management in a variety of preparations, comprising oral, ID, and topical applications **[6]**.

Oral Tranexamic Acid

TA has generally been utilized in oral administration at a dosage of 500 to 1,500 mg in 2 or 3 split daily doses, which is substantially lower than the normal amount to minimize severe hemorrhage **[30]**. The treatment duration has ranged from one month to six months in various trials. The alleviation of hyperpigmentation is usually seen one month following therapy. TA reaches peak plasma concentrations within 3 hours when taken orally and is unaffected by food in the GI tract. It can pass the blood–brain barrier and the placenta, although it is excreted in very small amounts in breast feeding.

Oral TA is a safe, effective melasma treatment regimen and has been used as a standalone agent or as a supplement to other treatment modality as topical, IPL and laser to ameliorate the activity of TA. **Karn et al. [31], Na et al. [32] and Minni and**

Poojary [33] investigated the effectiveness of oral TA in addition to standard topical therapy such as hydroquinone and sunscreen **[31]**, or oral TA at a dosage of 750 mg daily in addition to 2% topical TA **[32]** or combined with once daily fluocinolone-based triple combination cream [(FBTCC), acetonide 0.01%, tretinoin 0.05% and hydroquinone 2%] **[33]**. They concluded that the addition of oral TA to the treatment of melasma results in a quick and durable improvement. Moreover, oral tranexamic acid is a welcome addition to the arsenal of melasma treatment options, and it should be used in conjunction with a fluocinolone-based triple combination cream to achieve faster, longer-lasting results and avoid recurrence.

Shin et al. revealed that in conjunction with low-fluence quality-switched neodymium-doped yttrium aluminum garnet (QSNY) laser therapy, oral TA might show to be a safe and effective therapeutic option for melasma **[34]**. Agamia et al., demonstrated that melasma therapy with a low-fluence 1064-nm Qs-Nd: Yag laser is a safe and effective option. Including oral TA may improve clinical efficacy while reducing side effects or problems **[35]**.

Intradermal Tranexamic Acid

Direct injection into the dermis has been shown to benefit melasma patients. It can be given at a concentration of 4 mg/ml. The injections were spaced 1 cm apart, with 0.05 ml of TA injected at each site. TA with 2 mm microneedling at 2-week intervals for 6 sessions at a dose of 40 mg/ml maintenance **[15]**. **El Hadidi et al. [36]**, evaluated and compared the effectiveness of oral TA versus various dilutions of ID TA in melasma in 45 women cases. They demonstrated that Oral and intradermal microinjection of TA, independent of dilution, seem to be equally efficacious and safe in the management of melasma **[36]**.

Topical Tranexamic Acid

In addition to the oral formulation, a wide range of topical preparations and modalities have been utilized, which include TA 3% cream, 5% gel, 3% solution, or 5% liposome for 84 days **[3]**.

Unfortunately, TA's high potential for melasma treatment is hampered by its water-solubility (freely soluble) nature that causes pharmacokinetic limitations such as low diffusion across stratum corneum (SC), so one issue with current TA topical therapy is the lengthy treatment period required **[9]**. Generally, the low rate of drug diffusion across SC is a significant barrier to topical drug delivery. SC is the skin's outermost layer, and its structure is commonly likened to that of a brick wall, with the keratin-rich corneocytes functioning as the bricks and the cement of the intercellular lipid lamellae acting as the mortar **[10]**. Numerous strategies were employed to interrupt or destabilize the orderly inter - cellular lipids of the SC, including the use of methods that change the consistency of the SC, including ultrasound (US), microneedle (MN), and laser, as well as the use of vehicles and nanocarriers to enhance medication permeation **[10]**.

Several techniques were developed to enhance TA skin penetration, including the use MN **[37]**, Laser **[38]**, and intense pulsed light (IPL) **[39]**.

Topical TA with MN technology

Microneedle (MN) technology entails the formation of micron-sized channels in the skin that may facilitate the transport of water-soluble agent such as big proteins that do not traverse the skin barrier passively. Shamsi et al., and Zaky et al., demonstrated that a functional microarray of MN combined with topical TA solution proved the safety, a potential therapy for melasma, and did not vary from hydroquinone 4% **[37, 40]**.

Topical tranexamic acid with IPL

IPL is a broadband non-laser high intensity light sources that could be reach a wide variety of cutaneous tissues, particularly deeper pigmentation, and vasculature. Chung et al., examined the impact of topical TA in melsama During and after IPL treatment and revealed that topical TA may be utilized as a successful and safe complement to traditional melasma therapy **[39]**.

TA loaded Nanotechnology

Various kinds of nano-systems have recently been developed to enhance the dermal drug delivery. Vesicles systems are likely to be appropriate carriers owing to its physicochemical features, including as viscoelastic properties, size, and charge, that may be modified by changing lipid contents and manufacturing procedures. Moreover, comparing to complicated methods as IPL, MN and Laser, nanocarrier is simple technique for medication delivery. The main nanocarrier used to overcome the physicochemical limitations of TA and to increase its skin permeation are liposomes **[9]**, and emulsion **[41]**.

Liposomes are PL bilayer nano-vesicles that range in size from 20 nano-m to 10 micro-m. Since the 1980s, liposomal nano-carriers for topical medication administration have piqued the interest of researchers. Effective transdermal/topical drug delivery is heavily reliant on appropriate decrease of the barrier characteristics of the stratum corneum (SC); outermost layer skin barrier. Furthermore, their

capacity to shift medication disposition in the body may be a benefit in their employment as drug delivery carriers **[9]**.

Other proposed nanocarriers that used and was successful in ameliorating the skin permeation of other whiting agent and may has an impact on melasma treatment via encapsulating TA in the future plane are.

i. Invasomes (flexible liposome), Amnuaikit et al. examined the impact of Invasomes in enhancing the depigmentation effect of Phenylethyl resorcinol (PR) as well as safety and minimizing skin irritation, and they revealed that new treatment modality is safe, non-skin irritant, has stronger tyrosinase inhibitory effect, and reduces melanin level **[42]**.

ii. Transfersomes (deformable or elastic vesicles); Amnuaikit et al. demonstrated that In B16 melanoma cells, topical application of PR-loaded elastic vesicle carriers, have the efficiency to carry PR into the deep skin in both quantity and efficacy, which is superior to traditional liposomes and suited for a skin lightening solution. Furthermore, an acute irritation test in rabbits revealed that these formulations are safe for use on the skin **[42]**.

iii. Ethosomes (phospholipid rich ethanol nanovesicle); results of Limsuwan et al., indicated how ethosomes are able to effectively transport PR into the skin and have potential for topical administration of skin whitening agents **[43]**.

iv. Chitosan Nanocarrier: according to Zhang et al., chitosan nano-composites due to self-amphiphilic polymers are a useful and efficient PR delivery technology for hyperpigmentation treatment **[12]**.

Oral TA was generally well tolerated by patients, with even the most prevalent adverse effects being gastrointestinal (GIT) in nature. Deep vein thrombosis (DVT), acute renal cortical necrosis, acute myocardial infarction, and pulmonary embolism were uncommon, most likely because to the minimal oral TA dosage utilized. The most successful strategies should be investigated in future study for keeping benefits after TA therapy and by path oral side effects. Topical therapy is often recommended over systemic therapy for hyperpigmentation disorder because it delivers medicine directly to the diseased area, leading in less side effects and improved patient compliance **[6]**. Nonetheless, the SC, the main impediment to medication permeation, as a result, suggested nanotechnology melasma drug delivery system that can overcome the SC's barrier properties must investigated.

CONCLUSIONS

Despite technological advances and new medication formulations, melasma remains difficult to treat. Various TA formulations have been studied as a therapeutic modality for melasma over the years. Although topical and ID therapies haven't yet produced better outcomes, oral TA has. Recent research has begun to look into IPL, MN or laser-assisted drug delivery of topical TA. Future research directions should include loading TA in nanocarrier regimen such as lipid-based vesicles; Invasomes, transferosomes and ethosomes, which showed a promising outcome in term of safety with less side effects and high patients' acceptance. Large-scale, randomized, placebo-controlled studies are still needed to evaluate the effectiveness of TA in melasma and define the optimum manner of administration.

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