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REVIEW ARTICLE

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Tranexamic acid in treatment of melasma: A comprehensive review of clinical studies

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Abstract

Melasma is a human melanogenesis dysfunction that results in localized, chronic acquired hyperpigmentation of the skin. It has a significant impact on appearance, causing psychosocial and emotional distress, and reducing the quality of life of the affected patients. Tranexamic acid (TA) is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss and exerts its effect by reversibly blocking lysine binding sites on plasminogen molecules, thus inhibiting plasminogen activator (PA) from converting plasminogen to plasmin. As plasminogen also exists in human epidermal basal cells and cultured human keratinocyte are known to produce PA, there is basic rationale that TA will affect keratinocyte function and interaction. A thorough literature review indicates that while TA is used through various route of administration including oral, topical, and intradermal injection and as adjutant therapy with laser to treat melasma, its efficacy is not established adequately. Further studies are needed to clarify the role of TA in treatment of melasma.

KEYWORDS
hyperpigmentation, melasma, tranexamic acid

1 | INTRODUCTION

Melasma is a human melanogenesis dysfunction that results in chronic acquired and localized hyperpigmentation of the skin. It occurs symmetrically on sun exposed areas of the body and affects especially women of reproductive age (Miot, Miot, Silva, & Marques, 2009). Melasma is sometimes used interchangeably with the term "chloasma," which is a hyperpigmentation that often rise from pregnancy or changes in uterine and ovarian hormones. Melasma, however, can have a variety of possible causes (Gupta, Gover, Nouri, & Taylor, 2006). The exact causes of melasma are unknown, although some triggering factors are described, such as sun exposure, pregnancy, use of oral contraceptives and steroids, ovarian tumors, intestinal parasitoses, hepatopathies, use of cosmetics and photosensitizing drugs, procedures and inflammatory processes of the skin and stressful events (Elling & Powell, 1997; Katsambas & Antoniou, 1995; Miot et al., 2009; Sheth & Pandya, 2011; Tamega Ade, Miot, Bonfietti, Gige, Marques, & Miot, 2013). The objectives of melasma therapy should be protection from sunlight and depigmentation. First-line treatment usually consists of topical compounds that interfere with the melanin synthesis, broad-spectrum photoprotection, and camouflage. Chemical peels are often added in second-line therapy. Laser and light therapies represent potentially promising options for patients who are refractory to other modalities, but also carry a significant risk of worsening the disease (Shankar et al., 2014). Tranexamic acid (TA) is a plasmin inhibitor used to prevent fibrinolysis to reduce blood loss. It is a synthetic derivative of the amino acid lysine and exerts its effect by reversibly blocking lysine binding sites on plasminogen molecule, thus inhibiting plasminogen activator (PA) from converting plasminogen to plasmin. While plasminogen also exists in human epidermal basal cells and cultured human keratinocyte are known to produce PA, there is basic rationale that TA may be affect keratinocyte functions and interactions (Tse & Hui, 2013). Ultraviolet (UV) irradiation induces PA synthesis and increases plasmin activity in keratinocytes, the intracellular release of arachidonic acid, a precursor of prostanoids, and the level of alpha-melanocyte-stimulating hormone increase as the result of plasmin activity. These two substances can activate melanin synthesis. Therefore, the antiplasmin activity of TA is thought as the main mechanism of hypopigmentory effect of this agent (Ando, Matsui, & Ichihashi, 2010; Chang et al., 1993; Maeda & Naganuma, 1998; Takashima, Yasuda, & Mizuno, 1992; Wang, Zhang, Miles, & Hoover-Plow, 2004). Moreover, TA is found to be similar to tyrosine in the part of its structure, which can competitively inhibit tyrosinase enzyme activity (Li, Shi, Li, Liu, & Feng, 2010). Several forms of TA, including oral, topical, and localized

microinjection have been used to treat melasma. This study seeks to review the available literature discussing the efficacy of TA in treatment of melasma.

2 | METHODS

A literature search was performed using PubMed, Scopus, Medline, Embase, and the Cochrane database systematic reviews. Key words used as search terms were "Tranexamic acid," "Melasma," "Chloasma," "Pigmentation," "Hyperpigmentation," and "Lightening." No time limitation was considered in this review. Only English language articles were included. All studies that evaluated the effect of TA, in all route of administration, on melasema and hyperpigmentation were included.

3 | RESULTS

3.1 | Oral tranexamic acid

Nine studies discussing oral TA for treatment of melasma were found (see Table 1), comprising a total of 1,117 patients. Sample sizes ranged from 25 to 561 patients.

Kato et al. (2011) enrolled 32 women with senile lentigines with or without melasma in a randomized, parallel-group study to assess the prophylactic effect of TA against postinflammatory hyperpigmentation (PIH) caused by Q-switched ruby laser (QSRL). Patients on treatment arm ($n = 17$) received 750 mg TA per day for first 4 weeks after laser treatment. No significant difference in the incidence of PIH was shown between participants in two groups.

Karn, KC, Amatya, Razouria, and Timalsina (2012) in a prospective randomized controlled trial of 260 patients with melasma, assessed the efficacy of oral TA along with routine topical therapies including hydroquinone and sunscreen. TA was prescribed at a dose of 250 mg twice a day along with topical therapy for 3 months in group A ($n = 130$) while group B ($n = 130$) was treated only with topical preparations. Patients were followed up for another 3 months after treatment period and efficacy was measured based on Melasma Area and Severity Index (MASI). While statistically significant decrease in the mean MASI from baseline to 8 and 12 weeks was observed in group A, among group B the decrease in mean score was significant only at 8 weeks follow up. Patients rating for good to excellent outcome accounted 82.3% and 40.8% among group A and B, respectively.

Same year, Wu et al. (2012) enrolled 74 patients in their study and prescribed oral TA at a dosage of 250 mg twice daily for a therapeutic period of 6 months and followed up all patients for another 6 months after treatment. The effects of treatment were evaluated by two physicians independently based on improvement of pigmentation (excellent if >90%, good if >60%, fair if >30% and poor if <30%). The initial diminishment of melasma was detected after 1 month (82.4% patients) or 2 months (94.6% patients) of treatment. After 6 months of treatment, the total improvement rate was found among 95.9% of the subjects (10.8% excellent, 54% good, and 31.1% fair). After a 6 month follow-up, recurrence was seen in 9.5% of patients.

Also, Na et al. (2013) carried out a clinical study to elucidate the effects of oral TA in conjunction with topical TA on the melasma. Twenty-five women were instructed to take two TA tablets (each contained 125 mg of TA, 50 mg of ascorbic acid, 40 mg of L-cysteine, 4 mg of calcium pantothenate and 1 mg of pyridoxine chloride) three times a day along with the use of topical TA (2% TA and 2% naicinamide) twice a day for 8 weeks. The mean lesional melanin index (MI) scores and the erythema index (EI) scores was measured using a Mexameter® during each visit and skin biopsies were collected from eight subjects before and 8 weeks after treatment. Among 22 subjects that completed the study, both the lesional MI and EI scores decreased significantly. Considerably, both scores for the perilesional skin increased. Histological analysis showed significant reduction of epidermal pigmentation, vessel numbers and mast cell counts.

Aamir and Naseem (2014) performed a cross sectional study of 65 patients to evaluate the efficacy of oral TA in the treatment of melasma. Subjects were given 250 mg oral TA twice a day for 6 months and followed up for another 6 months. Results were measured by clinical and photographic assessment and were rated based on percentage of improvement like Wu et al study[17]. After 6 months of treatment, the total improvement rate was found among 98.5% of the subjects (23% excellent, 63% good, and 12% fair). Recurrence was seen in 12.3% of patients after follow-up period.

Li, Sun, He, Fu, He, and Yan (2014) enrolled 35 patients in a prospective open label study and prescribed 500 mg oral TA three times daily for 4 months. They used a 5-point scoring system in Skin Tone Color Scale to evaluate the severity of melasma at baseline, 4, 8, 12, and 16 weeks. Among 32 patients who completed the study, clinical manifestations revealed the color and size of skin lesions had significantly improved. From the objective evaluation of results, they found that the improved patients accounted for 85% in 4 weeks, 97% in 8 and 12 weeks, and 100% in 16 weeks.

Padhi and Pradhan (2015) enrolled 40 patients in an open labeled randomized trial to assess the efficacy of oral TA in addition to the triple combination cream containing fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 2% in melasma treatment. Group A patients ($n = 20$) were asked to apply the cream only and group B patients ($n = 20$) received oral TA 250 mg twice daily and applied the topical cream once daily for 8 weeks. Response was evaluated using MASI at baseline, 4 and 8 weeks. All patients completed the study. A faster reduction in pigmentation observed in combination therapy as compared to topical treatment alone at 4 and 8 weeks. The efficacy was maintained throughout the 6-month follow-up period.

Tan, Sen, Chua, and Goh (2016) evaluated the therapeutic effects of oral TA in the treatment of melasma refractory to topical skin-lightening agents in a retrospective study. The patients chosen had refractory melasma treated with oral TA 250 mg twice daily in addition to pre-existing combination topical therapy. Objective assessment using the physician's global assessment and MASI scores were performed based on a post hoc analysis of photographic records by three independent physicians. Altogether 25 patients were treated with TA for a mean period of 3.7 months (range 2–8 months). The mean MASI

TABLE 1 Oral TA in treatment of melasma

Study	Patient number	Assessment tool	Dose and duration	Control group	Placebo group	Result	Conclusion
Kato et al. (2011)	32	Clinical and colorimetric assessments	750 mg daily for the first 1 month after QSRL treatment	Yes	No	There was no significant difference in the incidence of PIH between participants who received oral TA and those who did not.	Oral TA may not be effective for preventing PIH after Q-switched ruby laser.
Karn et al. (2012)	260	MASI	500 mg daily for 3 months	Yes	No	Significant decrease in the mean MASI from baseline to 8 and 12	Addition of oral TA provides rapid and sustained improvement in the treatment of melasma.
Wu et al. (2012)	74	Clinical and photographic assessment	500 mg daily for 6 months	No	No	Patients rating for excellent, good, fair, and poor outcome accounted 10.8% ,54%, 31.1%, and 4.1% respectively	Oral TA is an effective and safe therapy for the treatment of melasma.
Na et al. (2012)	25	MI and EI scores	1,500 mg daily for 2 months	No	No	The MI and EI scores decreased significantly. Histological analysis showed significant reduction of epidermal pigmentation, vessel numbers and mast cell counts.	TA decreased epidermal pigmentation associated with melasma and also reversed melasma-related dermal changes, such as vessel number and increased numbers of mast cells.
Aamir and Naseem (2014)	65	Clinical and photographic assessment	500mg daily for 6 months	No	No	Patients rating for excellent, good, fair, and poor outcome accounted 23% ,63%, 12%, and 1.5% respectively	Oral TA is a safe and effective treatment in patients with melasma.
Li et al. (2014)	35	5-point scoring system in Skin Tone Color Scale	1,500 mg daily for 4 months	No	No	They found that the improved patients accounted for 85% in 4 weeks, 97% in 8 and 12 weeks, and 100% in 16 weeks.	Oral TA seems to be a potentially new and promising therapeutic option.
Padhi and Pradhan (2015)	40	MASI	500 mg daily and topical cream containing fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 2% once daily for 2 months	Yes	No	Faster reduction in pigmentation in combination group as compared to topical group was shown and the results were statistically significant at 4 weeks and 8 weeks	Addition of oral TA to fluocinolone-based triple combination cream results in a faster and sustained improvement in the treatment of melasma
Tan et al. (2016)	25	MASI	TA 500 mg daily in addition to pre-existing combination topical therapy	No	No	The mean MASI scores after TA treatment were significantly lower than those prior to treatment. The mean improvement in scores was 69%.	Low-dose oral TA can serve as a safe and useful adjunct in the treatment of refractory melasma.
Lee et al. (2016)	561	Physician Global Assessment	TA 250 mg twice a day for median of 4 months	No	No	89.7% patients had documented improvement, 10.0% remained unchanged, and 0.4% worsened.	Oral TA may be an effective adjunct for refractory melasma

TA = Tranexamic acid; PIH = postinflammatory hyperpigmentation; mMASI = Modified Melasma Area and Severity Index; MI = melanin index; EI = erythema index.

scores after TA treatment was 69% lower than at baseline with mean onset of lightening at 1.7 months. The follow-up period was up to 6 months. However, 72% of the patients had a relapse of melasma within 2 months of ceasing TA, despite continuing topical combination skin lightening agents.

Lee, Thng, and Goh (2016) conducted a retrospective analysis of patients who received oral TA for melasma. In all, 561 patients were enrolled. The degree of improvement was based on Physician Global Assessment. Duration of treatment was a median of 4 months (range 0.03–22 months) whereas the duration of follow-up was a median of 7 months (range 1–48 months).The dosage prescribed was 250 mg twice a day. In terms of treatment response, 89.7% of patients had documented improvement, 10% remained unchanged, and 0.4% worsened. Patients without family history of melasma had better response rates than those with family history. Of the 503 who improved, response was seen within 2 months of TA initiation (range 0.8–6 months), with a relapse rate of 27.2% with a median duration of 7 months on cessation of oral TA.

3.2 | Oral tranexamic acid with laser

Shin, Park, Oh, and Lee (2013) conducted a prospective randomized trial among 48 patients to evaluate the clinical efficacy and safety of oral TA combined with low-fluence 1064-nm quality-switched neodymium-doped yttrium aluminum garnet (QSNY) laser for the treatment of melasma. All patients were treated with two sessions of laser, and patients in the combination group took 8 weeks of oral TA-based medication(125 mg TA, 53 mg coated ascorbic acid, 40 mg L-cysteine, 4 mg calcium pantothenate, and 1 mg pyridoxine hydrochloric acid) three times per day. Two blinded dermatologists evaluated patients using the mMASI. Twenty three patients in the combination group and 21 in the laser group completed the study. The resulting data showed that a treatment regimen combining laser with oral TA led to a significantly greater reduction in mMASI score than laser treatment alone. Moreover, the number of patients graded as achieving improvements of greater than 50% and 75% that was significantly higher in the combination group, with no patients graded as having improved more than 75% in the laser-alone group.

In 2013, Cho, Choi, Cho, and Lee (2013) carried a controlled trial to evaluate the clinical efficacy and safety of oral TA as an adjuvant to intense pulsed light (IPL) and laser treatment in melasma. A total of 51 patients were included in the study. Patients were divided in group A ($n = 24$) that received oral TA 500 mg daily during IPL therapy and three or four times of low fluence QSNY laser treatments at 1–2 weeks interval and group B ($n = 27$) those who were treated with only IPL and laser. Patients have been on oral TA for at least 2 months (during treatments) and up to 8 months. Modified MASI scores were blindly evaluated by two investigators using digital photographs. In each group, changes in the mMASI score were statistically significant after treatments. Reduction of mMASI score was significantly higher in group A than group B.

3.3 | Topical tranexamic acid

Table 2 summarizes the clinical studies that have been evaluated the efficacy of topical TA in treatment of melasma. Five clinical studies with total of 144 patients and sample sizes ranged from 18 to 50 patients were found. In 1998, Maeda and Naganuma (1998) were found that post-exposure applications of 2 and 3% solutions of TA could prevent hyperpigmentation induced by UV exposure in guinea pigs. Histological analysis on skin biopsies revealed that melanin content in the basal layer of UV-exposed epidermis is significantly reduced in the regions to which TA solutions have been applied.

Steiner et al. (2009) enrolled 18 female with melasma in an open-label trial and randomly assigned them to receive either at home application of 3% TA cream twice a day (group A, $n = 8$) or intradermal injections of TA 0.05 ml (4 mg/ml) in 1 cm interval once per week for 12 weeks (group B, $n = 10$). Photographic evolution, MASI and self-assessment were used. Photographic evaluation showed improvement in 12.5% versus 66.7%, worsening in 50% versus 11.1%, and no change in 37.5% versus 22.2% in group A versus group B. For the MASI, there was significant improvement with no difference between treatments. About the self-assessment, 37.5% of patients rated melasma improvement as good and 50% as imperceptible in group A, while in group B, 66.7% rated improvement as good and 33.3% as imperceptible. In objective evaluation both treatments were effective, with no statistical difference between groups.

In 2012, a 12-weeks randomized double blind split-face trial involving 25 women by Kanechorn Na Ayuthaya, Niumphradit, Manosroi, and Nakakes (2012) assessed the efficacy of topical 5% TA versus vehicle for treatment of melasma. Patients applied topical TA or vehicle blindly to the designated sides of the face twice daily. Pigmentation and erythema were measured using MASI and Mexameter. Twenty one patients completed the study. Both MASI and MI improved significantly at 12 weeks as opposed to baseline in two groups of patients. However, the results did not reach statistical difference. Conversely, the EI at 12 weeks on the TA-treated side was higher than the vehicle. As previously mentioned Na et al. (2013) showed that combination of oral and topical TA decreased epidermal pigmentation associated with melasma and also reversed melasma-related dermal changes, such as vessel number and increased numbers of mast cells.

Ebrahimi and Naeini (2014) enrolled 50 patients with melasma in a double-blind, randomized, 12-week split-face trial. Patients applied 3% TA topical solution on one side of the face, and topical solution of 3% hydroquinone and 0.01% dexamethasone on the other side two times a day. The MASI was evaluated at baseline and every 4 weeks. The patient's self-assessment of melasma improvement was graded along four scales: excellent; >75% lightening, good; 51–75%, fair; 26–50% and poor; 0–25%. Thirty-nine patients successfully completed the trial. A significant decreasing trend was observed in the MASI score of both groups with no significant difference between them. Based on patients' self-assessment, 30% of patients using TA versus 39.4% of patients using combination solution possessed a favorable therapeutic response after 12 weeks (3% vs. 6.1% excellent, 27.3% vs. 33.3% good, 30.3% vs. 39.4% fair, and 39.4% vs. 21.2% poor). These differences were not

TABLE 2 Topical TA in treatment of melasma

Study	Patient number	Assessment tool	Dose and duration	Control group	Placebo group	Result	Conclusion
Steiner et al. (2009)	18	Photographic, MASI, colorimetry evolution	TA 3% cream twice a day or once weekly of intradermal injections with TA 0.05 ml (4 mg / ml) for 12 weeks.	Yes	No	In group A there was improvement in 12,5%, worsening in 50%, and no change in 37.5%. In group B, 66.7% of patients showed improvement, 11.1% worsening, and 22.2% remained unchanged. For the MASI, there was significant improvement with no difference between treatments	Although the subjective clinical evaluation has demonstrated the superiority of injection treatment, in objective evaluation both treatments were effective, with no statistical difference between groups
Kanechorn Na Ayuthaya et al. (2012)	23	MI score and MASI	5% TA gel or vehicle twice daily for 12 weeks.	Yes	Yes	MI and MASI scores were significantly reduced on both tested sides compare to baseline. However, lightening of pigmentation induced by TA gel was neither superior nor different compared to its vehicle although erythema was significant on the TA-applied site	Although lightening of pigmentation was obtained, the results were not significant between the two regimens
Ebrahimi et al. (2014)	50	MASI	3% TA topical solution or topical solution of 3% hydroquinone + 0.01% dexamethasone twice daily for 12 weeks.	Yes	No	A significant decreasing trend was observed in the MASI score of both groups with no significant difference between them. No differences were seen in patients' and investigator's satisfaction of melasma improvement between two groups.	The topical TA as an effective and safe medication for the treatment of melasma.
Banihashemi et al. (2015)	30	MASI	5% TA topical liposomeor 4% hydroquinone cream twice daily for 12 weeks	Yes	No	The mean MASI scores significantly reduced in both treated sides after 12 week. A greater decrease was observed with 5% liposomal TA, although this difference was not statistically significant.	Topical liposomal TA can be used as an effective and safe therapeutic agent in melasma.
Kim et al. (2016)	23	mMASI	2% TA formulation to the whole face twice daily for 12 weeks	No	No	The mMASI scores significantly improved in 22 of 23 participants after 12 weeks application	Topical TA is effective as a treatment for melasma.

TA = Tranexamic acid; mMASI = Modified Melasma Area and Severity Index; MI = melanin index.

statistically significant between two groups. However, the side effects of combined solution were significantly prominent compared with TA.

Banihashemi, Zabolinejad, Jaafari, Salehi, and Jabari (2015) compare therapeutic effects of liposomal TA and conventional hydroquinone dosage form on melasma. Thirty women were enrolled in a split-face trial lasting 12 weeks. Patients blindly applied 5% topical liposomal TA and 4% hydroquinone cream, to the designated sides of the face twice daily. Skin pigmentation was measured using MASI at each visit separately for each side at the baseline and every month until one month after treatment course. Twenty-three patients completed the study. The mean MASI scores significantly reduced in both treated sides after 12 week. A greater decrease was observed with liposomal TA, although this difference was not statistically significant.

Kim, Park, Shibata, Fujiwara, and Kang (2016) investigated the effects and mechanism of action of topical TA in the treatment of melasma. Twenty three patients applied a 2% TA emulsion to the whole face twice a day and the nonwoven fabric mask immersed in skin lotion containing 2% TA three times a week, for 12 weeks. Clinical effects were evaluated using the mMASI at baseline and weeks 4, 8, and 12 and skin pigmentation and erythema were measured using a chromameter. The mMASI scores significantly improved in 22 of 23 participants after application. The improvement was significant between baseline and week 4, and between weeks 4 and 8. The lightness values were increased and the erythema values were decreased in both lesional and perilesional normal skin. Histological evaluation of skin biopsies from 10 patients showed a significant decrease in melanin content in the epidermis. The number of CD31-positive vessels and the expression of the vascular endothelial growth factor both tended to decrease. Endothelin (ET)−1 was found to be downregulated with TA.

3.4 | Topical tranexamic acid with IPL

Chung, Lee, and Lee (2015) conducted a randomized, split-face study in 15 women who received a total of four sessions of IPL treatment on a monthly basis to both sides of the face. Topical 2% TA or vehicle was applied to a randomly assigned side during and after IPL treatment. Patients were followed up for 12 weeks after the last 4th IPL treatment. MI scores and mMASI were determined. Among 13 patients who completed the study, the mean MI and mMASI scores decreased significantly from baseline to 12 weeks after the last IPL treatment on the topical TA side but not on the vehicle side. The efficacy of topical TA in preventing rebound pigmentation after 12 weeks of the last IPL also revealed a statistically significant improvement on the topical TA side.

3.5 | Tranexamic acid microinjection and microneedling

Four clinical studies with total of 238 patients and sample sizes ranged from 18 to 100 patients that evaluated the effect of TA microinjection or microneedling on melasma were found.

In 2006, Lee et al (2006) conducted a prospective open-label study to assess the efficacy of localized microinjection of TA for the treatment of melasma. A total of 100 women were enrolled in study and 0.05 mL TA (4 mg/mL) was injected intradermally at 1 cm intervals. This was repeated weekly for 12 weeks. MASI was calculated at baseline and at 4, 8, and 12 weeks. Among 85 patients who completed the trial, a significant decrease in the mean MASI from baseline to 8 and 12 weeks was observed. Improvement after week 4 was more rapid than that during the first 4 weeks. According to the patients' self-assessment, 9.4% rated improvement as good (51 to 75% lightening), 76.5% as fair (26 to 50% lightening), and 14.1% as poor (0 to 25% lightening).

As previously mentioned, Steiner et al. (2009) compared the efficacy of topical 3% TA to intradermal injection of TA in 18 women with melasma. Based on MASI and colorimetric evaluation both treatment significantly improved melasma with no difference between treatments.

Li et al. (2010) used intradermal TA (5 mg/mL) on guinea pigs, which had been exposed to UVB for 1 month. Injection was performed every day for another month. The authors found that at the basal layer of exposed epidermis, the number of melanocytes was not reduced, but the melanin content was significantly lowered.

Budamakuntla et al. (2013) in a prospective open-label study randomly assigned 60 patients in ratio of 1:1 to localized microinjections of TA (4 mg/mL) or TA with microneedling (4 mg/mL). The procedures were done three times at monthly intervals (0, 4, and 8 weeks) and followed up for further 3 months. MASI scoring and patient global assessment was performed at monthly intervals. In the microinjection group, there was 35.72% improvement in the MASI score compared to 44.41% in the microneedling group, at the end of third follow-up visit. There was no significant difference in the mean MASI scores between the two groups. Six patients (26.09%) in the microinjections group, as compared to 12 patients (41.38%) in the microneedling group, showed more than 50% improvement. The scores revealed better improvement in patients treated with microneedling than with microinjections although the difference was not statistically significant.

Elfar and El-Maghraby (2015) enrolled 60 female in a clinical study to compare the efficacy of intradermal injection of TA ($n = 20$), topical silymarin cream ($n = 20$), and glycolic acid peeling 50% ($n = 20$) in treatment of melasma. TA was injected intradermaly 0.05 ml (4 mg/ml) into the melasma lesion at 1 cm interval weekly for 12 weeks. The patients were followed up monthly for 3 months after the last session. Clinical efficacy was categorized based on reduction in mMASI into five as excellent (if $> 75\%$), very good (50–75%), good (25–50%), poor ($< 25\%$), and no response (no change). The localized microinjection of TA significantly decreased the mMASI score from the baseline to the end of the treatment but it was less effective than silymarin cream and glycolic acid peeling. Good response in eight patients (40%), poor response in eight patients (40%), and no response in four patients (20%) were detected in TA treatment group.

4 | DISCUSSION

TA (oral, topical, or intralesional) used in treatment of melasma. In oral administration, it has been mostly used at dosage of 500 to 1,500 mg

in two or three divided doses daily, much lower than the usual dose to reduce excessive bleeding. The duration of therapy has varied in different studies ranging from 1 month to 6 months. Usually one month after treatment the improvement of hyperpigmentation might be seen. Oral TA has been used as stand-alone therapy or as an adjuvant to other topical treatment such as IPL and laser. However, as shown in Table 1, due to lack of placebo group in all of the clinical studies and lack of control group in more of them, further clinical studies need to elucidate the role of oral TA in treatment of melasma. Oral TA usually well tolerates and common side effects include gastrointestinal discomfort and menstrual irregularities (Aamir & Naseem, 2014; Karn et al., 2012; Lee et al., 2016; Wu et al., 2012). Serious potential side-effects such as deep vein thrombosis, massive pulmonary embolism and acute myocardial infarction are rare with the low dosages of TA used in the treatment of melasma (Lee et al., 2016).

Topical formulations of TA which have been used include 2% emulsion, 3% cream, 5% solution, and 5% liposomal cream. Of six clinical studies, only one of them did not show significant effect of topical TA for treatment of melasma. However, it is possible that the small sample size of this study or momentous effect of sun protection in melasma treatment resulted in the lack of statistically significant differences between TA and its vehicle. Topical application of TA was showed to be effective as well as topical hydroquinone alone, topical hydroquinone plus dexamethasone and intradermal injection of TA. Although topical TA is well tolerated and no severe side effects were reported, further clinical studies need to reveal the role of topical TA in treatment of melasma. Only one clinical study with small sample size showed beneficial effect of the addition of topical TA to IPL treatment of melasma.

Microinjection as well as microneedling of TA appears to be effective for treatment of melasma. No serious side effects apart from mild local discomfort, burning sensation and erythema were reported which mostly transient. Although several studies have been documented, large scale randomized controlled studies and long term follow-up studies are required in future. Furthermore as noted frequently most of these studies did not set positive and negative control group as well as TA treatment.

CONFLICT OF INTEREST

No conflict of interest.

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