Oral tranexamic acid in the prevention and treatment of hyperpigmentation disorders in skin of color: A scoping review

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KEY WORDS, PHRASES: oral tranexamic acid, hyperpigmentation, pigmentary disorders, melasma, skin of color

ABSTRACT

Background: Individuals with more richly pigmented skin face unique challenges due to increased susceptibility and recurrence of pigmentary alteration following skin inflammation, infection or injury. Recent research suggests that oral tranexamic acid (TXA) is a safe and effective means of treating pigmentary disorders. However, the efficacy and tolerability of TXA in those with Fitzpatrick skin types III-VI remains unexplored.

Methods: A systematic search was conducted using Scopus, Embase, Web of Science, and Cochrane Library databases from inception until August 2023 to investigate the efficacy and safety of oral TXA in the treatment, management, or prevention of pigmentary disorders.

Results: A total of 32 studies were included describing 2,715 individuals. Investigations in the treatment of melasma was most common, followed by other pigmentary disorders including lichen planus pigmentosus, solar lentigines, Riehl's melanosis, and post-inflammatory hyperpigmentation. Within the melasma cohort, assessments consistently indicated significant improvements amongst most studies. However, post-treatment recurrence was reported to be as high as 80%. Mixed levels of improvements were also reported for other pigmentary disorders, with most reports indicating moderate to good outcomes with no significant recurrence. Overall, oral TXA was largely well-tolerated, with adverse reactions most frequently including gastrointestinal discomfort, headaches, and menstrual irregularities.

Conclusions: Oral TXA has shown promise in treating pigmentary disorders in more richly pigmented skin; however, recurrence rates, notably in melasma patients, remain a concern. Further research into its role as an adjuvant therapy and determining optimal treatment duration could offer insights into reducing relapses.

INTRODUCTION

The study of skin of color has increasingly been recognized as an integral component in the field of dermatology due to the unique clinical presentations and therapeutic challenges posed by Fitzpatrick Skin Types (FST) III-VI. This group, primarily encompassing individuals from African, Native American, Asian, Middle Eastern, and Hispanic backgrounds, often exhibits dermatological manifestations that can differ significantly from lighter-skinned populations.[1] A prevalent concern among the population is pigmentary disorders, which can result from both intrinsic and extrinsic factors, such as inflammatory skin conditions, ultraviolet (UV) radiation exposure, and certain dermatological interventions.[2] In more richly pigmented individuals, a heightened susceptibility to pigmentary disorders may stem from differences in melanosome size and distribution.[3] These individuals face specific challenges in treating hyperpigmentation, particularly due to increased risk of post-inflammatory hyperpigmentation (PIH) and scarring from some conventional treatments.[4] Consequently, their distinct melanin biology demands a nuanced approach to therapy to ensure effective results without compromising skin quality. Beyond the aesthetic implications, pigmentary disorders have been shown to have significant psychosocial effects, highlighting the need for targeted and effective treatments.

Oral tranexamic acid (TXA) has emerged as a potential tool in the armamentarium against pigmentary disorders. Its anti-fibrinolytic properties have been extensively studied in relation to surgical and trauma scenarios.[5] However, recent research suggests that TXA's influence on melanogenesis and its capability to inhibit specific inflammatory mediators might offer significant dermatological benefits. Preliminary studies and clinical observations suggest its potential in reducing melanin synthesis, thereby ameliorating hyperpigmentation, particularly in those with FST III-VI. This scoping review sets out to meticulously examine and synthesize the current body of evidence related to the utilization of oral TXA for pigmentary disorders, particularly in skin of color. Herein, we explore in depth its therapeutic efficacy, safety profile, and prospective positioning in the framework of managing hyperpigmentation.

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MATERIALS AND METHODS

The scoping review was conducted in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR).[6] A scoping review design was chosen to permit evaluation of the full breadth of data in this area, as well as to identify gaps in the existing literature to direct future research.

Search Strategy

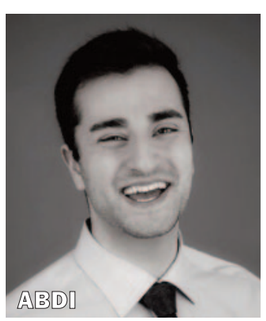
An initial search of Scopus, Embase, Web of Science, and Cochrane Library databases was performed from inception until August 2023 to identify articles on the topic. The search focused on studies that investigated the efficacy and safety of oral tranexamic acid in the treatment, management, or prevention of pigmentary disorders. To find target articles, we considered Medical Subject Headings (MeSH) as well as non-MeSH phrases. Principal search terms incorporated into the criteria included "oral tranexamic acid," "hyperpigmentary disorders,", "melasma", and "post-inflammatory hyperpigmentation". An exhaustive list of all search terms used is detailed in Table 1 in supplementary tables. If further data from a specific study was necessitated, the respective authors were contacted. To ensure no significant studies were overlooked, a manual search was also executed on the references list of related articles.

Eligibility Criteria

Following the electronic database search, studies were chosen according to predetermined criteria for inclusion: (1) Observational studies such as cohort, cross-sectional, or case-control studies and randomized controlled trials that investigate the safety and efficacy of oral tranexamic acid (TXA) for pigmentary disorders in patients of color; (2) The case group consisted of patients with pigmentary disorders, with 95% or greater of all individuals being assessed reported as being skin phototypes III-VI (including but not limited to individuals of African, Hispanic, Asian, Pacific Islander, Middle Eastern, and Indigenous); (3) Studies that reported either the reduction in hyperpigmentation severity using validated scales Melasma Area and Severity Index (MASI), modified Melasma Area and Severity Index (mMASI), Melanin Index (MI), Erythema Index (EI), Melasma Quality of Life Scale (MELASQoL) or through pre-determined Likert scales; (4) Provide sufficient raw data to understand the outcomes related to oral TXA treatment, including its efficacy and safety; (5) Studies conducted on human participants; and (6) Studies available in English. The criteria for excluding studies were: (1) Studies not reporting on the reduction in hyperpigmentation severity or not providing data on side effects/adverse events related to oral TXA use, or do not report on secondary outcomes such as quality of life or patient satisfaction; (2) Studies that did not report the skin phototype of participants; (3) Studies that included patients with skin phototype I-II without stratifying their outcomes separately; (4) Trials conducted on non-human subjects; and (5) reviews, commentaries, practice guidelines, or congress abstracts. There were no limitations on the selection of studies based on factors such as gender or geographical location.

Data Extraction

After the removal of duplicates, articles identified in the search were independently screened by two reviewers (VW, PA) using the Covidence systematic review software. If an article's abstract did not provide sufficient information to determine inclusion or exclusion, a full-text evaluation was conducted to confirm its eligibility. For the selected studies, data extraction was conducted by one reviewer (VW) and cross-verified by a second (PA). Disagreements between reviewers were settled through discussion. Extracted data included specific details such as authors, year of publication, study location, methodology, skin phototype, study population and sample, TXA intervention details, any comparators, primary and secondary outcomes, and adverse drug events. No critical appraisal was conducted, given the scoping nature of this review.



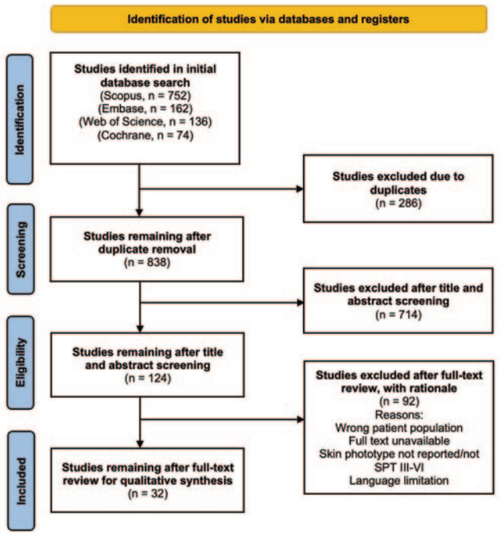


FIGURE 1: PRISMA flow chart

RESULTS

A systematic search was executed across Scopus, Embase, Web of Science, and Cochrane databases to identify pertinent articles related to oral TXA for the treatment of pigmentary disorders in skin of color. Following the removal of duplicates, 838 articles emerged. An initial screening of titles and abstracts led to the selection of 124 studies deemed potentially suitable for our review. Subsequent full-text examination narrowed this to 32 studies, which collectively described 2,489 individuals with pigmentary disorders that were treated with oral tranexamic acid. Figure 1 illustrates the PRISMA flow chart for study inclusion. These research articles spanned publication years from 2011 to 2023 and originated from diverse regions: North America (n=5), East Asia (n=12), South Asia (n=6), Middle East (n=3), and Africa (n=6). The results were categorized into two primary sections, namely "Melasma" and "Other Hyperpigmentation Disorders". The latter included studies related to lichen planus pigmentosus, solar lentigines, Riehl's melanosis, PIH after contact dermatitis, and prevention of PIH.

Melasma

Of the 32 included studies, 13 studies evaluated the efficacy of monotherapy oral TXA and 12 studies evaluated the efficacy of combination therapy (oral TXA and adjuvant), respectively. Adjuvant treatments consisted of f-TCC (fluocinolone-based triple combination cream consisting of hydroquinone, corticosteroid, and retinoid), low-fluence Q-switched Nd:YAG 1,064-nm laser (QS-Nd:YAG laser), CO_2 laser, 4% hydroquinone cream (HQ), and 20% azelaic acid cream. There was a total of 1,181 and 487 patients in these two groups with skin phototypes ranging from III-VI. Epidermal and mixed subtypes were the most common forms of melasma observed, with the centrofacial pattern being predominant. The standard dosing regimen was twice daily and did not differ significantly between the two groups, with daily dosages ranging from 250 to 750 mg. Both monotherapy and combination therapy using oral TXA consistently indicated significant improvements of varying levels amongst most studies.

Follow-up was conducted within 10 studies in the single-use group and ranged from 1 month to 1 year. Recurrence rates at follow-up timepoints conducted longer than 3 months ranged from 4% to 45%. One study reported a rebound rate, defined as greater mMASI scores than pre-treatment baselines, to be as high as 10%.[7] In the combination group, follow-up was reported in nine groups, ranging from 1 month to 6 months. Recurrence rates past the three-month post-treatment period ranged from 4% to 80%, with rebound rates as high as 20%.[7] Comparison of efficacy between monotherapy oral TXA with intralesional TXA (4 mg/mL or 100 mg/mL) and topical hydroquinone 4% yielded mixed results, with three studies demonstrating that the effect of oral TXA was superior to control groups,[8–10] and three studies demonstrating no significant difference.[11–13] Four studies compared the efficacy of adjuvant treatments against a monotherapy oral TXA-only control group, consisting of 4% HQ topical treatment (n=2), f-TCC (n=1), and QS-Nd: YAG laser (n=1). All combination therapy studies demonstrated significant improvement compared to monotherapy groups.[7,14–16]

Regarding safety profiles, TXA was largely well-tolerated. Only four individuals discontinued treatment due to severe abdominal pain, headache, nausea, vomiting, and edema of the hands and feet.[9,17] The most frequent adverse reactions reported included gastrointestinal discomfort, headaches, and menstrual irregularities. A few rare side effects were also noted, such as numbness in the lower extremities and transient amnesia. Importantly, there were no thromboembolic events, including deep vein thrombosis, pulmonary embolism, arterial thrombosis, or stroke reported in any of the studies. A more comprehensive breakdown of findings can be seen in Table 2 and 3 in supplementary tables.

Other Pigmentary Disorders

Two studies reported on using TXA in lichen planus pigmentosus, both from Morocco. Treatments ranged from 250 mg QD to 500 mg BID, with patients mostly of Fitzpatrick skin types III-IV. A mix of good to moderate improvements were observed, with no noted recurrence or adverse effects. For solar lentigines, one study from Thailand used 1,500 mg once daily (QD) of TXA over 6 weeks. Assessments indicated varied improvements, with hypomenorrhea as a side effect. Riehl's Melanosis was evaluated in two studies from South Korea and China. Treatments ranged from 250 mg QD to 250 mg BID. Most patients showed significant improvements, and no adverse effects were reported. PIH after contact dermatitis was evaluated in two studies from Singapore and South Korea. Gradual or substantial clinical clearance was consistently observed post-TXA treatments, with no reported adverse effects. In PIH prevention, three studies from Japan, China, and the USA were assessed. Treatment outcomes varied, with duration of use up to 3 months. A high proportion of patients showed significant improvement, with no adverse effects reported. A detailed summary of findings is outlined in Table 4 in supplementary tables.

DISCUSSION

The clinical utility of oral TXA for pigmentary disorders, especially in individuals with skin of color, is an evolving area of investigation. Beyond its well-documented antifibrinolytic properties, TXA holds significance in managing hyperpigmentation. Its potent inhibitory effect on plasmin affects UV light-induced activation of this enzyme, reducing plasminogen binding to keratinocytes.[18] In the hyperpigmentary cascade, activated plasmin prompts keratinocytes to release potent mediators such as alpha-melanocyte-stimulating hormone (alpha-MSH) and prostaglandin E2. These in turn, stimulate melanocyte tyrosinase, the principal enzyme driving melanin synthesis, thereby intensifying skin hyperpigmentation.[18] Moreover, the antiangiogenic attributes of TXA, notably its capacity to attenuate plasmin-mediated expression of vascular endothelial growth factor (VEGF) and endothelin-1, shed light on its therapeutic promise, especially in disorders like melasma, where vascular elements play a contributing role.[19,20]

From the studies included in this scoping review, there is empiric evidence supporting the efficacy of oral TXA in improving pigmentary disorders in skin of color. Both isolated and adjuvant TXA treatments demonstrated benefit at reducing hyperpigmentation, with minimal adverse events. However, in our evaluation of the included studies, there was noticeable variance in the reported hyperpigmentation measures. While many reports on melasma consistently utilized the MASI score as a standardized measure, other pigmentary conditions lacked such uniformity in their evaluative metrics, and outcomes interpretation may be inconsistent. MI and EI, although occasionally reported, was an infrequent measure used in the studies. The heterogeneity in outcome measures underscores the need for a more standardized approach to assessing pigmentary conditions in future research.

Although prior literature has explored the efficacy of oral TXA in treating pigmentary disorders, our scoping review distinguishes itself by specifically examining its impact in populations with skin of color with an added evaluation on recurrence and adverse events.[21] A previous publication has reported on the management of post-inflammatory hyperpigmentation in skin of color.[22] However, it was limited in scope and did not explore the potential benefits of oral tranexamic acid in depth. Additionally, there have been reviews dedicated to treatments for melasma on darker skin types.[23] Our work stands distinct by exploring the nuanced responses and unique challenges of managing pigmentary disorders presenting in individuals of color in the context of TXA treatment, highlighting the need for greater inclusive and comprehensive dermatological research.

While the administration of oral TXA for pigmentary disorders has varied in dosage, prior publications evaluating doses ranging from 500-1,500 mg have showed no pronounced difference in efficacy.[24] Similarly, results from our review support no discernable dose-dependent differences in efficacy. In conjunction with traditional and newer therapeutic methods, TXA has exhibited significant efficacy, particularly for moderate to severe melasma. Our results also suggest that adjuvant therapy may be more effective than monotherapy with oral TXA particularly amongst people of color. More research is warranted to quantitatively evaluate the effect size and adverse effects of these adjuvant therapies, specifically the use of lasers, and the potential risk of post-treatment hyperpigmentation in skin of color.[25]

Research continues to explore the benefits of oral TXA, including alternative routes of administration, notably topical applications. The shift toward topical use signifies the broader dermatological drive to refine treatment methodologies with minimal potential systemic adverse effects. However, while there is an increasing body of evidence supporting topical administration, limitations of these studies include their sample sizes and methodology consistency.[26] A key challenge remains in determining the efficacy of topical TXA in penetrating the skin's lipid-rich layers.[27] Further trials to elucidate its bioavailability, clinical effectiveness, and how it measures against other modes of administration for managing pigmentary disorders would be beneficial. Our results demonstrate that relapse is common and highlights the potential need for more extended periods of treatment particularly in people of color. However, data regarding recurrence rates in more richly pigmented individuals is limited and emphasizes the need to better capture the phenomenon when treating hyperpigmentation.

Considering the exploratory design of this review, no critical appraisal was conducted of the included studies. A limitation of this study is that we were unable to more objectively quantify the effect of oral TXA on pigmentary disorders because of current heterogeneity in outcome measures within the included studies. The limited available literature investigating pigmentary conditions, apart from melasma in skin of color, further restricted our capacity to derive robust clinical inferences on the safety and efficacy of oral TXA.

CONCLUSION

The results of our scoping review suggest that oral TXA is effective in addressing pigmentary disorders in patients of color. Treatment using TXA alone or in combination approaches consistently demonstrated significant improvements in hyperpigmentation, with minimal adverse events rarely causing treatment discontinuation. However, recurrence was commonly reported and highlights the potential need for more extended periods of use. Additional research is warranted to better characterize the recurrence of hyperpigmentation following medication discontinuation, and to improve our understanding of the possible dose-outcome relationship with the use of oral TXA in the treatment of pigmentary disorders in skin of color.

SUPPLEMENTARY TABLES

Supplementary tables can be found below.

Table 1
Table 2
Table 3
Table 4

DECLARATIONS

I. Funding: No funding was provided for the preparation of this

study.

II. Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

III. Availability of data and material: All data was collected through peer-reviewed publications available in the public domain. The authors of the papers were contacted if any information was missing, and they were asked to provide information on any contradicting, omitted, or ambiguous data.

IV. Ethics approval: No ethical review was necessary for the study because the data were taken from already-published works.

V. Consent to participate: Not applicable.

VI. Consent for publication: Not applicable.

VII. Code availability: Not applicable.

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Supplemental Material

Table 1: Keywords and search terms used in the systematic review and meta-analysis.
Abbreviations: *Ti, title. Ab, abstract. Kw, keywords. TS, topic (encompasses title, abstract, author keywords, keywords plus)*

Database	Search terms
Scopus	((TITLE-ABS-KEY ("tranexamic acid" OR TXA OR Cyklokapron OR Lysteda OR Transamin OR Espercil OR Exacyl OR Hemaplex OR Tranex) AND (oral) AND ("hyperpigmentation" OR melasma OR chloasma OR "pregnancy mask" OR "post-inflammatory hyperpigmentation" OR PH OR lentigines OR "age spots" OR "liver spots" OR freckles OR "Riel melanosis" OR "cafe-au-lait spots" OR "Addisons disease" OR "drug-induced hyperpigmentation" OR "erythema dyschromicum perstans" OR "poikiloderma of Civatte" OR hemochromatosis OR "Peutz-Jeghers syndrome" OR "Laugier-Hunziker syndrome" OR "fixed drug eruption" OR "minocycline-induced hyperpigmentation" OR "tinea versicolor" OR "postradiation hyperpigmentation" OR "eczema craquele" OR "dermatitis neglecta" OR "Nevus of Ota" OR "Horis nevus" OR "Beckers nevus" OR "linea nigra" OR "acanthosis nigricans" OR "lichen planus pigmentosus" OR "Mongolian spots" OR "stasis dermatitis" OR "periorbital hyperpigmentation" OR phytophotodermatitis OR "berloque dermatitis" OR "post-laser hyperpigmentation" OR "Nevus of Ito" OR "Idiopathic guttate hypomelanosis" OR "perioral dermatitis" OR "candida-associated hyperpigmentation" OR "macular amyloidosis" OR "melanoma-associated hyperpigmentation" OR "pigmented purpuric dermatosis"))
Cochrane	('tranexamic acid':ti,ab,kw OR 'txa':ti,ab,kw OR 'cyklokapron':ti,ab,kw OR 'lysteda':ti,ab,kw OR 'transamin':ti,ab,kw OR 'espercil':ti,ab,kw OR 'exacyl':ti,ab,kw OR 'hemaplex':ti,ab,kw OR 'tranex*':ti,ab,kw) AND 'oral':ti,ab,kw AND ('hyperpigmentation':ti,ab,kw OR 'melasma':ti,ab,kw OR 'chloasma':ti,ab,kw OR 'pregnancy mask':ti,ab,kw OR 'post-inflammatory hyperpigmentation':ti,ab,kw OR 'pih':ti,ab,kw OR 'lentigines':ti,ab,kw OR 'age spots':ti,ab,kw OR 'liver spots':ti,ab,kw OR 'freckles':ti,ab,kw OR 'riehl melanosis':ti,ab,kw OR 'cafe-au-lait spots':ti,ab,kw OR 'addisons disease':ti,ab,kw OR 'drug-induced hyperpigmentation':ti,ab,kw OR 'erythema dyschromicum perstans':ti,ab,kw OR 'poikiloderma of civatte':ti,ab,kw OR 'hemochromatosis':ti,ab,kw OR 'peutz-jeghers syndrome':ti,ab,kw OR 'laugier-hunziker syndrome':ti,ab,kw OR 'fixed drug eruption':ti,ab,kw OR 'minocycline-induced hyperpigmentation':ti,ab,kw OR 'tinea versicolor':ti,ab,kw OR 'postradiation hyperpigmentation':ti,ab,kw OR 'eczema craquele':ti,ab,kw OR 'dermatitis neglecta':ti,ab,kw OR 'nevus of ota':ti,ab,kw OR 'horis nevus':ti,ab,kw OR 'beckers nevus':ti,ab,kw OR 'linea nigra':ti,ab,kw OR 'acanthosis nigricans':ti,ab,kw OR 'lichen planus pigmentosus':ti,ab,kw OR 'mongolian spots':ti,ab,kw OR 'stasis dermatitis':ti,ab,kw OR 'periorbital hyperpigmentation':ti,ab,kw OR 'phytophotodermatitis':ti,ab,kw OR 'berloque dermatitis':ti,ab,kw OR 'post-laser hyperpigmentation':ti,ab,kw OR 'nevus of ito':ti,ab,kw OR 'idiopathic guttate hypomelanosis':ti,ab,kw OR 'perioral dermatitis':ti,ab,kw OR 'candida-associated hyperpigmentation':ti,ab,kw OR

Database	Search terms
	'macular amyloidosis':ti,ab,kw OR 'melanoma-associated hyperpigmentation':ti,ab,kw OR 'pigmented purpuric dermatosis':ti,ab,kw)
Web of Science	TS=("tranexamic acid" OR TXA OR cyclokapron OR lystedt OR transamine OR especial OR exacly OR hexaplex OR tranes) AND TS=(oral) AND TS=("hyperpigmentation" OR "melasma" OR "cloasma" OR "pregnancy mask" OR "post-inflammatory hyperpigmentation" OR PIH OR "lentigines" OR "age spots" OR "liver spots" OR "freckles" OR "Richl melanosis" OR "cafe-au-lait spots" OR "Addisons disease" OR "drug-induced hyperpigmentation" OR "'erythema dyschromicum perstans" OR "poikiloderma of Civatte" OR "hemochromatosis" OR "Peutz-Jeghers syndrome" OR "Laugier-Hunziker syndrome" OR "fixed drug eruption" OR "minocycline-induced hyperpigmentation" OR "tinea versicolor" OR "postradiation hyperpigmentation" OR "eczema craquele" OR "dermatitis neglecta" OR "Nevus of Ota" OR "Horis nevus" OR "Beckers nevus" OR "linea nigra" OR "acanthosis nigricans" OR "lichen planus pigmentosus" OR "Mongolian spots" OR "stasis dermatitis" OR "periorbital hyperpigmentation" OR "phytophotodermatitis" OR "berloque dermatitis" OR "post-laser hyperpigmentation" OR "Nevus of Ito"' OR "Idiopathic guttate hypomelanosis" OR "perioral dermatitis" OR "candida-associated hyperpigmentation" OR "macular amyloidosis" OR "melanoma-associated hyperpigmentation" OR "pigmented purpuric dermatosis")
Embase	('tranexamic acid':ti,ab,kw OR 'txa':ti,ab,kw OR 'cyklokapron':ti,ab,kw OR 'lysteda':ti,ab,kw OR 'transamin':ti,ab,kw OR 'espercil':ti,ab,kw OR 'exacyl':ti,ab,kw OR 'hemaplex':ti,ab,kw OR 'tranex*':ti,ab,kw) AND 'oral':ti,ab,kw AND ('hyperpigmentation':ti,ab,kw OR 'melasma':ti,ab,kw OR 'chloasma':ti,ab,kw OR 'pregnancy mask':ti,ab,kw OR 'post-inflammatory hyperpigmentation':ti,ab,kw OR 'pih':ti,ab,kw OR 'lentigines':ti,ab,kw OR 'age spots':ti,ab,kw OR 'liver spots':ti,ab,kw OR 'freckles':ti,ab,kw OR 'riehl melanosis':ti,ab,kw OR 'cafe-au-lait spots':ti,ab,kw OR 'addisons disease':ti,ab,kw OR 'drug-induced hyperpigmentation':ti,ab,kw OR 'erythema dyschromicum perstans':ti,ab,kw OR 'poikiloderma of civatte':ti,ab,kw OR 'hemochromatosis':ti,ab,kw OR 'peutz-jeghers syndrome':ti,ab,kw OR 'laugier-hunziker syndrome':ti,ab,kw OR 'fixed drug eruption':ti,ab,kw OR 'minocycline-induced hyperpigmentation':ti,ab,kw OR 'tinea versicolor':ti,ab,kw OR 'postradiation hyperpigmentation':ti,ab,kw OR 'eczema craquele':ti,ab,kw OR 'dermatitis neglecta':ti,ab,kw OR 'nevus of ota':ti,ab,kw OR 'horis nevus':ti,ab,kw OR 'beckers nevus':ti,ab,kw OR 'linea nigra':ti,ab,kw OR 'acanthosis nigricans':ti,ab,kw OR 'lichen planus pigmentosus':ti,ab,kw OR 'mongolian spots':ti,ab,kw OR 'stasis dermatitis':ti,ab,kw OR 'periorbital hyperpigmentation':ti,ab,kw OR 'phytophotodermatitis':ti,ab,kw OR 'berloque dermatitis':ti,ab,kw OR 'post-laser hyperpigmentation':ti,ab,kw OR 'nevus of ito':ti,ab,kw OR 'idiopathic guttate hypomelanosis':ti,ab,kw OR 'perioral dermatitis':ti,ab,kw OR 'candida-associated hyperpigmentation':ti,ab,kw OR 'macular amyloidosis':ti,ab,kw OR 'melanoma-associated hyperpigmentation':ti,ab,kw OR 'pigmented purpuric dermatosis':ti,ab,kw)

Tables

Table 1: *Summary of included studies evaluating the use of monotherapy oral tranexamic acid in melasma treatment.*
Abbreviations: *RCT: Randomized Controlled Trial, F: Female, M: Male, SPT: Skin Phototype, GI: Gastrointestinal, EI: Erythema Index, MI: Melanin Index, Sp-MELASQOL: Spanish Melasma Quality of Life Scale, MASI: Melasma Area and Severity Index, mMASI: Modified Melasma Area and Severity Index, DVT: Deep Vein Thrombosis, QD: Once Daily, BID: Twice Daily, TID: Three Times Daily, QOL: Quality of Life. IL: intralesional*

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence Rates	Adverse Effects
Simpson 2022[28]	USA	Retrospective chart review	42 (40F, 2M)	F:48.3 M:55.5	III-VI	-	-	325 BID	1-40 months (avg 12 months)	Likert scale	45.2% of patients had excellent or good outcomes	-	-	Headache (2.4%), GI discomfort - diarrhea, nausea, discomfort (4.8%), hypermenorrhea (2.4%), hypomenorrhea (2.4%), rhinorrhea (2.4%), numbness in lower body, 2.4%)
Elkamshoushi 2022[7]	Egypt	RCT	20F	35.1	III-V	-	-	250 BID	3 months	mMASI reduction	35.9% mean mMASI improvement after 3 months treatment; no significant mMASI difference due to recurrence at the 6-month mark	6 months	45% recurrence, 10% rebound (greater than baseline values); no significant decrease compared to pre-treatment baseline	Gastritis (15.0%)
ElHadidi 2021[11]	Egypt	RCT	14F	40.9	III-IV	-	-	250 BID	2 months	mMASI reduction, EI, MI	43% reduction in mMASI, significant reduction in MI, EI; ; no significant difference	1 month	None; continued to show improvement from post-treatment (mMASI	Abdominal discomfort and nausea (33.3%), hypomenorrhea 27% (patients were also perimenopausal)

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence Rates	Adverse Effects
											compared to IL TXA cohorts (4 mg/mL and 100 mg/mL)		reduction 48%)	
Agamia 2021[15]	Egypt	RCT	30F	36	III-V	Centrofacial (40%), malar (6.7%), mandibular (53.3%)	Epidermal (13.3%), dermal (6.7%), mixed (80%)	250 QD	3 months	mMASI value	significantly decreased mMASI from baseline	3 months	recurrence not reported, mMASI still significantly decreased from baseline, mild increase from end of treatment	Minimal, no severe side effects
ArreolaJauregui 2020[16]	Mexico	Retrospective chart review	27 (-)	-	II-V (3.77% II)	-	-	650 QD	5 months	mMASI reduction, Sp-MELASQOL	46% reduction in mMASI, 29% reduction in Sp-MELASQOL	-	-	Breast pain, abdominal pain, arthralgia, hypo-oligomenorrhea
Yaghoobi 2019[12]	Iran	RCT (assessor-blinded)	29 (28F, 1M)	37	II-V (5% type II)	Centrofacial (72.4%), malar (24.1%), mandibular (3.4%)	Epidermal (58.6%), dermal (10.3%), mixed (31.0%)	250 BID	4 months	MASI	Significant reduction in mean MASI from baseline; no significantly difference from 4% HQ group	3 months	mildly increased MASI from 12 weeks, still significantly decreased from pre-treatment baseline	GI side effects (10.3%), hypomenorrhea (44.8%), both (6.9%)
Khurana 2019[8]	India	Randomized open-label comparative study	32 (26F, 6M)	-	IV-V	Centrofacial (59.37%)	Epidermal (18.8%), dermal (9.4%),	250 BID	3 months	mMASI reduction	Significantly reduced mMASI (57.48%); all	3 months	6.3% recurrence	Gastritis (6.3%), oligomenorrhea (3.1%)

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence Rates	Adverse Effects
							mixed (71.9%)				32 patients in the oral group (100%) showed >50% improvement, out of which 8 showed >75% improvement; significant improvement compared to IL TXA (4 mg/mL)			
Sharma 2017[9]	India	RCT	39 (-)	n/a	IV-V	Centrofacial (78%), malar (20%), mandibular (1%)	Epidermal (64%), dermal (18%), mixed (18%)	250 BID	4 months	mMASI reduction	Significant reduction in mean mMASI by 12 weeks; 100% of patients showed at least a good response (>50% in mMASI score); significant improvement compared to IL TXA (4 mg/mL)	12 weeks	4% recurrence	Mild epigastric discomfort (5.1%, resolved with ranitidine), hypomenorrhea (15.4%)
Lee 2016[29]	Singapore	Retrospective chart review	561 (513F, 48M)	40.7	III-IV	-	-	250 BID	4.5 months	Likert scale, degree of improvement based on Physician	Improvement in majority (89.7%) of patients;10.0% had no	48 weeks	27.2% recurrence	GI discomfort - bloating, pain, nausea and vomiting (14), headache (6), tinnitus (3), facial numbness (1), lip numbness (1), finger/toe

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence Rates	Adverse Effects
										Global Assessment (% lightening)	improvement, 0.4% worsened. Patients without family history of melasma had better response rates than those with family history (90.6% vs 60.0%); no significant improvement compared to IL TXA (4 mg/mL)			numbness (1), transient amnesia (1), tremors (1), hypomenorrhea/ oligomenorrhea (3), dysmenorrhea (1), DVT (1), acral pruritus (2), facial hypertrichosis (1), lip swelling (1), palpitations (1), worsening necrobiosis lipoidica (1), periorbital swelling (1), increased hair loss (1)
Li 2014[30]	China	Prospective open-label study	32 (-)	41	III-IV	-	-	250 TID	4 months	Likert scale	100% demonstrated improvement; 75% demonstrated marked improvement; 100% reported improvement in QOL	-	-	GI discomfort (12.5%), oligomenorrhea (6%)
Aamir 2014[31]	Pakistan	Cross-Sectional	65 (56F, 9M)	36	III-IV	Centrofacial (12%), malar (33.8%), mandibular (3%),	Epidermal (61.5%), dermal (15.3%), mixed (23%	250 BID	6 months	Likert scale	86% had excellent or good outcomes	6 months	12% recurrence	Oligomenorrhea (7.1%), stomach upset (3%), palpitations (3%)

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence Rates	Adverse Effects
						mixed (50.8%)								
Wu 2012[32]	China	Prospective clinical trial	74F	-	III-V	-	-	250 BID	6 months	Likert scale	95.9% of subjects demonstrated at least fair improvement (melasma decreased by >30%). 64.8% demonstrated at least good improvement (melasma decreased by 60%).	6 months	9.5% recurrence	GI discomfort (5.4%), hypomenorrhea (8.1%), rare: skin rash, dizziness, alopecia, drowsiness, hyposexuality
Karn 2012[10]	Nepal	RCT	130 (109F, 21M)	30.3	III-V	Centrofacial (78.5%), frontal (11.5%), chin (10.0%)	Epidermal (71.5%), dermal (10.8%), mixed (17.7%)	250 BID	4 months	MASI, Patient satisfaction score	Significant reduction in mean MASI from baseline; significant improvement compared to HQ control group	-	-	-

Table 2: *Summary of included studies on the use of oral tranexamic acid combined with adjuvant treatments for melasma patients.*
Abbreviations: *F: female, RCT: randomized controlled trial, BID: twice daily, QD: once daily, mMASI: modified Melasma Area and Severity Index, MQoL: Melasma Quality of Life, MI: melanin index, TID: three times daily, HQ: hydroquinone, ND:YAG: neodymium-doped yttrium aluminum garnet, DLQI: Dermatology Life Quality Index, MASI: Melasma Area and Severity Index, EI: erythema index, Sp-MELASQOL: Specific Melasma Quality of Life Scale, PIH: post-inflammatory hyperpigmentation, GI: gastrointestinal, TXA: tranexamic acid, SPT: skin phototype*

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Adjuvant Treatment	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence	Adverse Effects
Martinez-Rico 2022[14]	Mexico	RCT (with crossover at midpoint)	43F	-	III-V (4.5% II)	-	-	325 BID	Fluocinolone-based triple combination cream (fluocinolone acetonide 0.01%; tretinoin 0.05%; and hydroquinone 2%)	4 months	mMASI, MQoL, MI	Significantly decreased mMASI, MQoL, and MI from baseline; combination treatment led to significantly reduced scores in both treatment arms	-	-	TXA: oligomenorrhea, GI discomfort. Cream: burning, erythema, xerosis
Perveen 2022[33]	Pakistan	RCT	30 (-)	-	III-V	-	-	250 BID	Fluocinolone-based triple combination cream	2 months	MASI reduction	76.5% reduction in MASI from baseline; significant reduction compared to triple combination cream group	-	-	No serious side effects
Elkamshoushi 2022[7]	Egypt	RCT	20F	32.4	III-V	-	-	250 BID	4% HQ cream qHS	3 months	mMASI reduction	Significant reduction in mean mMASI (77.5% reduction); only this	6 months	20% recurrence, 0% rebound, still significant improvement	Itching (65.0%), erythema (45.0%)

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Adjuvant Treatment	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence	Adverse Effects
												treatment group retained significantly reduced mMASI at 6-month mark		from pre-treatment baseline	
			20F	31.8	III-V	-	-	250 BID	1064 nm low-fluence Q-switched ND: YAG laser (2 sessions, one month apart)	3 months	mMASI reduction	Significant reduction in mean mMASI (24% reduction) after 3 months treatment; no significant mMASI difference due to recurrence at the 6-month mark	6 months	Recurrence in 80%, rebound in 20%, lowered compared to pre-treatment baseline but not significant	Itching (20%), PIH (15%)
Akl 2022[34]	Egypt	RCT	25F	36.6	III-V	Centrofacial (56%), malar (32%), mandibular (12%)	Epidermal (36%), dermal (24%), mixed (40%)	250 QD	20% azelaic acid	3 months	mMASI reduction, DLQI	Significant improvement in mMASI and DLQI (66.96%, 70.8%); significantly reduced scores compared to 4% HQ group	6 months	12% recurrence	No serious side effects

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Adjuvant Treatment	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence	Adverse Effects
			25F	35.2	III-V	Centrofacial (52%), malar (28%), mandibular (20%)	Epidermal (40%), dermal (28%), mixed (32%)	250 QD	4% HQ cream	3 months	mMASI reduction, DLQI	Significant improvement in mMASI and DLQI (59.31%, 60.33%)	6 months	4% recurrence	No serious side effects
Behrangi 2022[35]	Iran	RCT	20 (-)	43.3	III-IV	-	-	250 TID	1064 nm low-fluence Q-switched ND: YAG laser (every 2 weeks)	3 months	MASI value, EI	Significantly decreased MASI scores and EI	1 month	Continual improvement from end of treatment, significant from baseline	GI upset (19%), hypomenorrhea (5%)
Agamia 2021[15]	Egypt	RCT	30F	37.5	III-V	Centrofacial (66.7%), malar (20%), mandibular (13.3%)	Epidermal (20%), dermal (6.7%), mixed (73.3%)	250 QD	1064 nm low-fluence Q-switched ND: YAG laser (every 2 weeks)	3 months	mMASI value	Significant reduction in mean mMASI; no significant difference compared to IL TXA with laser group	3 months	Recurrence not reported, mild increase in mMASI from end of treatment (still significant from baseline)	No severe side effects
Minni 2020[36]	India	RCT (triple-blinded)	61 pts	38.5	III-VI	Centrofacial (55.4%), malar (44.6%), mandibular (0%)	Epidermal (38.5%), dermal (49.2%), mixed (12.3%)	250 BID	Oral ranitidine 150 BID, triple combination cream (2% HQ)	3 months	mMASI, Sp-MELASQOL	Significant reduction in mean mMASI (77.5% reduction); significant improvement compared to monotherapy TXA group	3 months	18.0% recurrence	Acidity (14.8%), diarrhea (1.6%), abdominal pain (1.6%), vomiting (1.6%), hypomenorrhea (3.2%), PIH (3.2%)

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Adjuvant Treatment	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence	Adverse Effects
ArreolaJauregui 2020[16]	Mexico	Retrospective chart review	26 (-)	-	II-V (3.77% II)	-	-	650 QD	4% HQ cream	5 months	mMASI reduction, Sp-MELASQOL	61% reduction in mMASI, 49% reduction in Sp-MELASQOL; significant improvement compared to monotherapy TXA group	-	-	Breast pain, abdominal pain, arthralgia, hypo-oligomenorrhea
Cho 2013[37]	South Korea	Retrospective chart review	51F	39.6	III-IV	-	-	500 QD	1064 nm low-fluence Q-switched ND: YAG laser	3 months	mMASI	Significantly reduced mMASI; significant improvement compared to laser only group	-	-	No serious side effects
Shin 2013[38]	South Korea	RCT	19F	-	III-V	-	-	750 QD	1064 nm low-fluence Q-switched ND: YAG laser (every month)	2 months	mMASI, clinical improvement–based quartile grading scale:	Significant reduction in mean mMASI; significant improvement compared to laser only group	-	-	No serious side effects
Lajevardi 2017[17]	Iran	RCT	33	35.4	II-IV (2.2% II)	-	-	250 TID	4% HQ cream	3 months	Photographic Assessment + MASI	Significant reduction in MASI; significant improvement compared to	3 months	30% recurrence (26% in control, no sig diff in rates)	3 patients discontinued due to: severe abdominal pain, flank pain, edema of hands and feet,

Study	Country	Study Design	Demographic	Mean Age (years)	SPT	Melasma Pattern	Melasma Subtype	Dose of TXA (mg)	Adjuvant Treatment	Duration of Treatment	Evaluation	Outcome	Follow-up Period	Recurrence	Adverse Effects
												HQ only group			nausea, vomiting, or headache
Kim 2022[39]	USA	Retrospective chart review	6F	52.8	III-IV	-	-	325 BID	Fractional CO2 + laser toning	1 month	mMASI	The CO_2 laser therapy with the TXA cohort showed the largest decrease in mean mMASI. Patients who started on oral TXA earlier showed better clinical improvement	-	-	1 patient with hyperpigmentation

Table 1: *Summary of included studies on the use of oral tranexamic acid in treating various pigmentary conditions, including lichen planus pigmentosus, solar lentigines, Riehl's melanosis, PIH after contact dermatitis , and the prevention of PIH.*
Abbreviations*: F: female, M: male, QD: once daily, BID: twice daily, RCT: randomized controlled trial, Nd:YAG: neodymium-doped yttrium aluminum garnet, RMV: relative melanin value, LI: luminance index, MI: melanin index, EI: erythema index, TXA: tranexamic acid, PIH: post-inflammatory hyperpigmentation, SPT: skin phototype*

LICHEN PLANUS PIGMENTOSUS													
Study	**Country**	**Design**	**Demographic**	**Mean Age**	**SPT**	**Dose**	**Adjuvant**	**Duration**	**Measured by**	**Outcome**	**F/U period**	**Recurrence**	**Adverse Effects**
Zenjari 2020[40]	Morroco	Prospective Study	20 (18F, 2M)	49	III-IV	250 QD	None	4-6 months (avg 5.7 months)	Likert scale	5 (good improvement), 5 (moderate improvement), 3 (no improvement), 7 (lost to follow-up)	6 months	No recurrence	None
Benchikhi 2019[41]	Morocco	Case Series	11 (10F, 1M)	50.9	III-IV	500 BID	Topical hydroquinone, high potent corticosteroid	3-6 months	Clinical assessment	Good result in three patients, remaining patients are still being treated	-	No recurrence	None
SOLAR LENTIGINES													
Study	**Country**	**Design**	**Demographic**	**Mean Age**	**Fitzpatrick**	**Dose**	**Adjuvant**	**Duration**	**Measured by**	**Outcome**	**F/U period**	**Recurrence**	**Adverse Effects**
Rutnin 2019[42]	Thailand	RCT (double-blinded)	20 (19F, 1M)	52.8	III-V	1500 QD	532-nm Q-Switched Nd:YAG Laser	6 weeks	Colorimetry (RMV, LI), dermoscopy, digital photographs (blinded dermatologist + patient evaluation)	RMV, LI decreased at 6 weeks (significance not reported). RMV lower but not significantly different TXA vs control at 6/12 weeks, LI not significantly different between control and TXA, TXA group had lower incidence of dermoscopic finding of pigmented granules at 6/12 weeks (corresponds w PIH), physician assessment: no difference between two groups but both showed 14 (placebo) and 18 (TXA) showed >50% improvement by 6th week. Similar results via patient assessment	6 weeks	Mild increases in RMV and LI from 6th week, statistical significance not reported	Hypomenorrhea

RIEHL'S MELANOSIS													
Study	**Country**	**Design**	**Demographic**	**Mean Age**	**Fitzpatrick**	**Dose**	**Adjuvant**	**Duration**	**Measured by**	**Outcome**	**F/U period**	**Recurrence**	**Adverse Effects**
Kwon 2017[43]	South Korea	Prospective pilot study	8F	47.4	III-V	250 QD	1064 nm low-fluence Q-switched ND: YAG laser, hydroquinone cream	104 weeks	Clinical assessment, MI, and EI	37% of patients with > 75% improvement and 63% of patients with 51–75% improvement. The mean MI and EI values at the final visit also showed a significant decrease compared with baseline (MI: $76.3 \pm 25.3 \rightarrow 45.2 \pm 17.6$; EI: $23.5 \pm 6.8 \rightarrow 16.7 \pm 5.2$) ($p < 0.05$).	-	-	-
Xu 2019[44]	China	Prospective pilot study	10 (-)	-	III-V	250 BID	50 mg Glycyrrhizin TID	6 months (3 months compound, then 3 months of only TXA)	Melanin Index (MI) + Erythema Index (EI) + 5-Grade Scale	70% had marked improvement (51-75), 20% moderate improvement, 10% minimal improvement; Mean MI decreased from (94.7 + 7.0) to (63.8 + 9.4) at 6 months; Mean EI decreased from (29.7 + 2.1) to (14.4 + 2.0) at 6 months	-	-	None
PIH AFTER CONTACT DERMATITIS													
Study	**Country**	**Design**	**Demographic**	**Mean Age**	**Fitzpatrick**	**Dose**	**Adjuvant**	**Duration**	**Measured by**	**Outcome**	**F/U period**	**Recurrence**	**Adverse Effects**
Lee 2016[13]	Singapore	Case report	1F	64	IV	750 QD	1064 nm low-fluence Q-switched ND: YAG laser (ten sessions)	10 weeks	Clinical evaluation	Substantial improvement	1 year	No recurrence	-
Shin 2018[45]	South Korea	Case series	2 (1F, 1M)	57.5	III	Not reported	-	-	Clinical clearance	Gradual Clearance with treatment and discontinuation of henna product	-	-	-
PREVENTION OF PIH													

Study	Country	Design	Demographic	Mean Age	Fitzpatrick	Dose	Adjuvant	Duration	Measured by	Outcome	F/U period	Recurrence	Adverse Effects
Kato 2011[46]	Japan	Randomized parallel-group study	15F	-	III-IV	750 mg QD	694.5-nm Q-switched ruby laser	4 weeks	Total Improvement (Based on MI)	Treatment with TXA did not influence change in TI, no change in PIH between groups	-	-	-
Sun 2018[47]	China	Prospective cohort study	896 (835F, 61M)	22	III-IV	0.5 mg BID	0.3 glutathione TID	3 months	Grade of improvement by physicians and patients (4-point scale)	99.66% exhibited >=51% improvement. Average improvement 3.71 of 4.00	-	-	-
Lindgren 2021[48]	USA	Case Series	2F	29	III-IV	650mg BID	Case 1: Clobetasol 0.05% cream BID; case 2: topicals (sunscreen and tretinoin 0.05%) and daily spironolactone 100 mg	8 weeks	Clinical assessment	Use of oral TXA following an acute injury was both safe and effective in preventing PIH among at-risk individuals.	16 weeks	No recurrence	none