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Topical Treatments for Melasma: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background: Melasma is an acquired skin disease characterized by symmetric hyperpigmentation on sun-exposed areas, particularly on the face. Recently, there has been tremendous scientific interest in novel, safe, and effective topical agents to manage melasma.
Objective: To evaluate topical treatments for melasma and provide evidence-based recommendations for clinical use and further research.
Methods: We performed a systematic review of randomized controlled trials (RCTs) on topical agents for the treatment of melasma on March 4th, 2019 using PRISMA guidelines. Clinical recommendations were based on the American College of Physicians guidelines.
Results: After screening, we identified 35 original RCTs using azelaic acid, cysteamine, epidermal growth factor, hydroquinone (liposomal-delivered), lignin peroxidase, mulberry extract, niacinamide, *Rumex occidentalis*, triple combination therapy, tranexamic acid, 4-n-butylresorcinol, glycolic acid, kojic acid, aloe vera, ascorbic acid, dioic acid, ellagic acid and arbutin, flutamide, parsley, or zinc sulfate for melasma.
Conclusions: Cysteamine, triple combination therapy, and tranexamic acid received strong clinical recommendations for the treatment of melasma. Cysteamine has excellent efficacy and is reported to have anti-cancer properties, but has not been directly compared with hydroquinone. Triple combination agents and tranexamic acid are effective, but carry theoretical risks for ochronosis and thrombosis, respectively. Natural compounds are associated with low risk for adverse events, but more research is needed to determine the efficacy, optimal formulation, and appropriate concentration of novel treatments.

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INTRODUCTION

Melasma is an acquired skin disease characterized by symmetric patches of hyperpigmentation on sun-exposed areas such as the cheeks, forehead, chin, nose, and upper lips. Histological features may include epidermal and dermal pigmentation, solar elastosis, increased vascularization, and mastocytosis.[1]

Although the true incidence of melasma is unknown, melasma has been reported to affect 1% to 50% of the population globally.[2] Melasma is more prevalent in female patients of Asian, Latin American, Middle Eastern, and African descent due to multifactorial causes including increased skin pigmentation, alterations in hormone levels, family history, and sun exposure.[3-6] Melasma has a tremendous societal and psychosocial impact as patients with melasma report dramatically lower self-esteem, depression, and social isolation.[7,8]

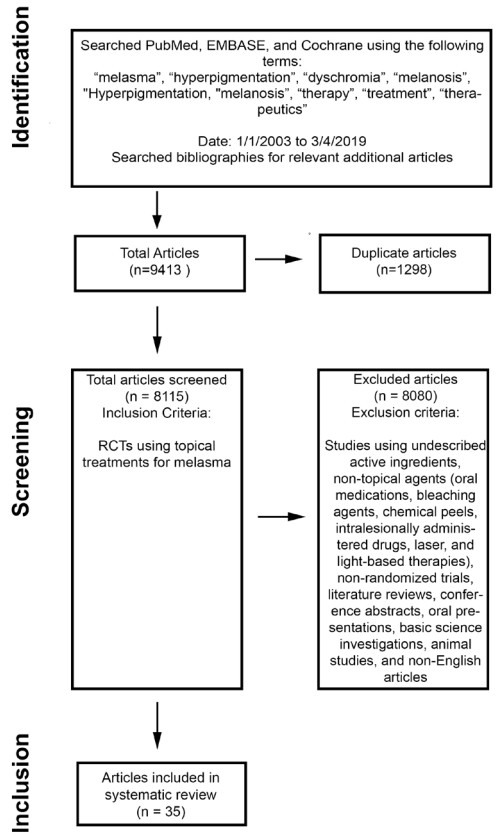
Therapy for melasma remains a clinical challenge and topical agents are the mainstay. First-line topical treatment options for melasma are hydroquinone (HQ) and triple combination (TC) therapies, which include HQ, a retinoid, and a steroid. Second-line treatments include chemical peels and laser therapies.[9] There have been concerns about the long-term safety and efficacy of HQ. Topical HQ is associated with ochronosis, a bluish-gray discoloration of the skin.[9] In response, HQ has been banned in the European Union as a cosmetic additive, but is available as a prescription medication.[9]

Recently, there has been tremendous scientific and general public interest in novel, safe, and effective topical agents to improve melasma. To determine the safety and efficacy of newer topical agents for melasma, we performed a systematic review of randomized controlled trials (RCTs) on topical agents for the treatment of melasma and provided evidence-based recommendations for clinical use and further research.

METHODS

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol, we performed a systematic search for novel and currently used topical treatments for melasma on March 4th, 2019 (Figure 1). Included articles were RCTs using topical treatments for melasma published within the

FIGURE 1. *PRISMA* Systematic search strategy. We performed a systematic search on March 4th, 2019, according to *PRISMA* guidelines.



last 15 years (since January 1st, 2003) as this period was considered clinically relevant. Clinical recommendations were based on the American College of Physicians (ACP) guidelines.[10] We excluded studies using proprietary or undescribed active ingredients (as these studies and outcomes would not be verifiable or reproducible by third parties, if desired) and those evaluating non-topical agents (ie, oral medications, bleaching agents, chemical peels, intralesionally administered drugs, laser, and light-based therapies) as stand-alone or combination approaches. Patients were allowed to apply daily sunscreen in the included studies. Non-randomized original reports, literature reviews, conference abstracts, oral presentations, basic science investigations, animal studies, and non-English articles were excluded. We examined the bibliographies of included published original reports and literature reviews to ensure that relevant articles were included in the systematic search.

RESULTS

Our systematic search identified 9,413 articles. After screening titles, abstracts, and full text articles, we identified 35 original RCTs using azelaic acid (2), cysteamine (2), epidermal growth factor (EGF) (1), liposomal hydroquinone (1), lignin peroxidase (1), mulberry extract (1), niacinamide (1), *Rumex occidentalis* (1), tranexamic acid (TXA) (5),TC therapy (5), 4-*n*-butylresorcinol (3), glycolic acid (2), kojic acid (2), aloe vera (1), ascorbic acid (1), dioic acid (1), ellagic acid and arbutin (1), flutamide (1), parsley (1), or zinc sulfate (2) for melasma. Table 1 provides a detailed summary of the identified studies and highlights study designs, treatment parameters, results, and adverse events (AEs).

TABLE 1.

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Benefits outweigh risks and burden											
Azelaic acid											
Farshi[11]	OL	29	Not reported (Iran)	8 weeks	MASI	None	Twice daily for 8 weeks	20% azelaic acid	7.6 ± 3.5	3.8 ± 2.8#	Erythema, irritation, and pruritus
								4% HQ	7.2 ± 3.2	6.2 ± 3.6	Erythema, irritation, and pruritus
Mazurek[12]	OL	60	I-III (Poland)	24 weeks	Colorimetry using Mexameter® (pigment within lesion)	Skin hydration, elasticity, erythema	Twice daily for 24 weeks	10% azelaic acid, 10% d-panthenol	25.0U	19.5 U*	Not reported
								5% azelaic acid, 5% pyruvic acid	16.0 U	13.0 U*	Not reported
								20% azelaic acid, 10% mandelic acid, 5% phytic acid, 5% 4-n-butyl resorcinol, 2% ferulic acid	19.6 U	12.5 U*	Not reported

TABLE 1. CONTINUED

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Benefits outweigh risks and burden											
Cysteamine											
Mansouri[14]	DB, PC	50	III and IV (Iran)	16 weeks	Colorimetry using Mexameter (relative melanin value)	MASI, IGA	Once daily for 16 weeks	5% cysteamine	75.2 ± 37	26.2 ± 16#	Erythema, dryness, itching, burning sensation, and irritation
								Placebo	68.9 ± 31	60.7 ± 27.3	None
Farshi[13]	DB, PC	40	III and IV (Iran)	16 weeks	Colorimetry using Dermacatch (difference between pigmented and normal skin)	MASI, IGA	Once daily for 16 weeks	5% cysteamine	72.3 ± 27.8	23.8 ± 12.9#	Erythema, dryness, itching, burning sensation, and irritation
								Placebo	52.9 ± 16.4	50 ± 18	None
Epidermal growth factor											
Lyons[17]	DB, PC, SF	15	Not reported (California, USA)	8 weeks	Physician GAIS	MelasQoL, PSA	Twice daily for 8 weeks	EGF	--	Improvement in 73.4% of patients	None
								Placebo	--	Improvement in 13% of patients	None
Benefits outweigh risks and burden											
Hydroquinone (Liposome-encapsulated)											
Taghavi[18]	DB, SF	20	III and IV (Iran)	16 weeks	MASI	None	Once daily for 12 weeks	4% HQ	10.73 ± 4.7	6.07 ± 3.8*	Not reported
								4% liposomal HQ	10.73 ± 4.7	6.25 ± 4.0*	Not reported
Lignin Peroxidase											
Draelos[19]	SF, SB	30	I-IV (North Carolina, USA)	12 weeks	MASI	Colorimetry, dermatospectrophotometer, IGA, PSA	Twice daily for 12 weeks	Lignin peroxidase	Not reported	No difference between groups	None
								4% HQ	Not reported	--	None
Draelos[19]	SF, SB	30	I-IV (North Carolina, USA)	12 weeks	MASI	Colorimetry, dermatospectrophotometer, IGA, PSA	Twice daily for 12 weeks	Lignin peroxidase	Not reported	Significant improvement*	None
								No treatment	Not reported	--	None
Mulberry extract											
Alvin[20]	SB, PC	50	III-V (Philippines)	8 weeks	MASI	Colorimetry, MelasQoL	Twice daily for 8 weeks	75% mulberry extract oil	4.076 ± 0.24#	2.884 ± 0.25*#	Mild itching
								Placebo	3.484 ± 0.52	3.392 ± 0.53	Mild pruritus and erythema

TABLE 1. CONTINUED

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Niacinamide											
Navarrete-Solis[22]	DB, SF	27	III-V (Mexico)	8 weeks	MASI	Chromameter, IGA, infrared thermography, histological sections	Every 3 hours during daytime for 8 weeks	4% niacinamide	3.7 (95% CI: 2.9–4.4)	1.4 (95% CI: 3.3–4.7)*	Erythema, pruritus, and burning
								4% HQ	4 (95% CI: 90.9–1.8)	1.2 (95% CI: 0.8–1.6)*	Erythema, pruritus, and burning
***Rumex occidentalis* (Western Dock)**											
Mendoza[23]	DB, SF	45	Not reported (Philippines)	8 weeks	MASI	Colorimetry, IGA, PSA	Twice daily for 8 weeks	3% *R. occidentalis* cream	Not reported	0.60 ± 0.86 decrease*	Mild peeling
								4% HQ	Not reported	0.55 ± 0.62 decrease*	None
								Placebo	Not reported	0.09 ± 0.12 decrease	None
Tranexamic acid											
Atefi[26]	DB	60	Not reported (Iran)	12 weeks	MASI	Patient satisfaction	Twice daily for 12 weeks	5% TXA	4.80 ± 1.06	2.33 ± 0.71*	None
								2% HQ	4.37 ± 0.93	2.30 ± 0.65*	Erythema and skin irritation
Banihashemi[27]	SF, DB	23	III-V (Iran)	16 weeks	MASI	None	Twice daily for 12 weeks	5% liposomal TXA	14.72 ± 2.2	6.78 ± 2.9*	None
								4% HQ	14.60 ± 2.3	7.60 ± 2.2*	Skin irritation
Ebrahimi[28]	SF, DB	39	Not reported (Iran)	12 weeks	MASI	IGA, PSA	Twice daily for 12 weeks	3% TXA	31.68 ± 10.32	10.76 ± 9.43*	Erythema, skin irritation, xerosis, and scaling
								3% HQ and 0.01% dexamethasone	29.52 ± 11.72	10.48 ± 7.84*	Erythema, skin irritation, dryness of the skin, scaling, hypertrichosis, and inflammation
Kanechorn Na Ayuthaya[25]	DB, SF, VC	21	Not reported (Thailand)	12 weeks	MASI	Colorimetry, IGA, PSA	Twice daily for 12 weeks	5% TXA	Not reported	Significant improvement from baseline, non-significant difference between groups	Minor skin irritation
								Vehicle	Not reported	--	Minor skin irritation

TABLE 1. CONTINUED

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Viyoch[24]	DB, VC	60	IV (Thailand)	8 weeks	Colorimetry using Mexameter® (relative melanin value)	MASI, moisture content, pH, erythema	Twice daily for 8 weeks	6.5% TXA	80.6 ± 19.7	59.4 ± 17.4*#	Erythema, scaling, burning and/or stinging
								Vehicle	74.4 ± 17.3	75.4 ± 16.3	Erythema, edema, burning and/or stinging
Triple Combination											
Ferreira Cestari[32]	OL	119	II-V (Brazil)	8 weeks	Proportion of patients with complete clearance	IGA, PSA, tolerability	Once daily for 8 weeks	4% HQ, 0.05% RA, and 0.01% FA	--	35%#	Erythema, burning sensation, desquamation, telangiectasia, and headache
							Twice daily for 8 weeks	4% HQ	--	5.1%	Erythema, burning sensation, desquamation, telangiectasia, and headache
Chan[33]	SB	242	II-V (East and Southeast Asia)	8 weeks	Global Severity Score (GSS) at 8 weeks	GSS at 4 weeks, MASI, IGA, PSA, patient satisfaction	Once daily for 8 weeks	4% HQ, 0.05% RA, and 0.01% FA	100% of patients with GSS of moderate or severe	64.2% of patients with GSS of none or mild*#	Erythema, irritation, exfoliation, and discomfort
							Twice daily for 8 weeks	4% HQ	100% of patients with GSS of moderate or severe	39.4% of patients with GSS of none or mild*#	Erythema, irritation, exfoliation, and discomfort
Taylor[34]	SB	641§	I-IV (Multicenter, USA)	8 weeks	Proportion of patients with complete clearance	Proportion of patients with complete or near-complete clearance	Once daily for 8 weeks	HQ 4%, 0.05% RA, and 0.01% FA	--	26.1%#	Erythema, desquamation, burning, dryness, and pruritus
								0.05% RA and 4% HQ	--	9.5%	Erythema, desquamation, burning, dryness, and pruritus
								0.05% RA and 0.01% FA	--	1.9%	Erythema, desquamation, burning, dryness, and pruritus
								4% hydroquinone and 0.01% FA	--	2.5%	Erythema, desquamation, burning, dryness, atrophy and pruritus

TABLE 1. CONTINUED

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Gong[30]	DB, PC	211	Not reported (China)	8 weeks	Decreased Index of Total Target Score (DITTS)¶	Improvement rate of target skin melanin (by spectrophotometer), integral therapeutic efficacy rate	Once daily for 8 weeks	4% HQ, 0.05% RA, and 0.01% FA	--	0.48 ± 0.21#	Erythema, stabbing pain, peeling, telangiectasia, burning, dry skin, itching, sensation of thin skin, and redness/swelling
								Placebo	--	0.10 ± 0.14	Burning, dry skin, tautening, and itching
Astaneh[31]	DB	32	III-V (Iran)	12 weeks	Investigator's subjective assessment	None	Once daily for 12 weeks	4% HQ	--	31.3% of patients with good to excellent results	Erythema and scaling
								4% HQ, 0.05% RA, and 0.05% dexamethasone	--	81.2% of patients with good to excellent results #	Erythema and scaling#
4-*n*-butylresorcinol											
Huh[38]	DB, SF, VC	20	III-V (South Korea)	8 weeks	Colorimetry using Mexameter®	None	Twice daily for 8 weeks	0.1% 4-*n*-butylresorcinol	206.85 ±31.60	196.20 ±28.42#	Mild erythema and itching
								Vehicle	205.77 ±33.74	209.80 ±32.19	None
Huh[39]	DB, SF, VC	23	Not reported (South Korea)	8 weeks	Colorimetry using Mexameter®	PSA	Twice daily for 8 weeks	0.1% liposome-encapsulated 4-*n*-butylresorcinol	200.68 ± 38.24	185.42 ± 38.81#	None
								Vehicle	201.13 ± 39.78	194.43 ± 39.03	None
Khemis[40]	DB, SF, VC	30§	III-V (France)	12 weeks	Clinical pigmentation score	Colorimetry, tolerability, skin acceptability, investigator's assessment of improvement, PSA	Twice daily for 12 weeks	0.3% 4-*n*-butylresorcinol	7.5 ± 1.	6.2 ± 2.3#	Mild stinging, burning, pruritus, erythema, dryness, peeling and desquamation
								Vehicle	7.5 ± 1.9	6.7 ± 2.1	Depigmentation

TABLE 1. CONTINUED

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Benefits closely balanced with risks											
Glycolic acid											
Guevara[43]	VC, DB	35	III-V (Texas, USA)	12 weeks	MASI and colorimetry using Mexameter®	IGA, PSA	Twice daily for 12 weeks	4% HQ, 10% buffered glycolic acid, vitamins C and E, and sunscreen	Not reported	Significant improvement in MASI and Mexameter score from baseline and between groups	Burning, itching, redness, dryness, peeling, edema, and scaling
								Vehicle (sunscreen only)	Not reported	--	Burning, itching, redness, dryness, peeling, and scaling
Ibrahim[44]	SB, PC	100	Not reported (Egypt)	12 weeks	mMASI	IGA, PSA, digital image analysis, dermoscopy	Once daily for 12 weeks	4% HQ	12.410 ± 3.915	5.740 ± 5.713*	Burning, itching, redness, dryness, peeling, edema, and scaling
								4% HQ and 10% glycolic acid	10.030 ± 2.456	6.060 ± 4.550*	Erythema, erosion, scaling, and crusting
								4% HQ and 0.01% hyaluronic acid	11.600 ± 4.447	4.080 ± 3.041*	Pruritus
								4% HQ, 0.01% hyaluronic, and 10% glycolic acid	12.570 ± 5.522	3.430 ± 3.336*	Pruritus, erythema, scaling, and crusting
								Placebo	10.540 ± 2.699	10.540 ± 2.699	None
Kojic acid											
Deo[45]	SB	80	IV and V (India)	12 weeks	MASI	IGA, PSA, therapeutic response according to ΔMASI	Once daily for 12 weeks	1% kojic acid	9.145 ± 7.69	3.57 ± 3.04*	Burning
								1% kojic acid and 2% HQ	8.38 ± 4.92	2.09 ± 1.62*	Burning
								1% kojic acid and 0.1% betamethasone valerate	11.02 ± 7.33	7.58 ± 6.493	None
								1% kojic acid, 2% HQ, and 0.1% betamethasone valerate	15.61 ± 9.03	7.115 ± 7.03*	Acneiform eruptions

TABLE 1. CONTINUED

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Monteiro[46]	--	60	Not reported (India)	12 weeks	MASI	None	Twice daily for 12 weeks	0.75% kojic acid cream and 2.5% vitamin C	11.177 ± 6.4817	8.773 ± 5.6743*	Erythema
								4% HQ	15.613 ± 9.6626	4.334 ± 3.5709*#	Erythema and mild burning
Risks and burden outweigh benefits											
Parsley											
Khosravan[47]	DB	54	Not reported (Iran)	8 weeks	MASI	None	Once daily for 8 weeks	Parsley (brewed 2.5 g in 125 ml of water) every week	6.66 ± 4.39	4.92 ± 3.07*	Redness and itching
								4% HQ	6.68 ± 3.24	5.06 ± 2.66*	Redness and itching
Zinc Sulfate											
Iraji[48]	SB	55	Not reported (Iran)	6 months	MASI	PSA	Twice daily for 6 months	10% zinc sulfate solution	5.7 ± 3.2	5.1 ± 2.9*	Not reported
								4% HQ	6.4 ± 3.4	3.3 ± 2.4*#	Not reported
Yousefi[49]	DB	82	Not reported (Iran)	5 months	MASI	None	Once daily for 2 months	10% zinc sulfate	6.3 ± 2.1	5.1 ± 2.0*	Mild post-inflammatory hyperpigmentation, irritation
								4% HQ	6.4 ±1.6	3.9 ± 1.4*#	Irritation
Insufficient evidence to determine net benefit											
Aloe Vera											
Ghafarzadeh[50]	DB	180	Not reported (Iran)	5 weeks	MASI	None	Not reported	*Aloe vera* gel extract	15.5 ± 2.4	13.9 ± 2.7	None
								Liposome-encapsulated *Aloe vera* gel extract	15.0 ± 1.8	10.2 ± 2.0#	None
Ascorbic Acid											
Espinal-Perez[51]	DB	180	IV and V (Mexico)	16 weeks	PSA and colorimetry using DermaSpect®	Digital photograph and regular color slides	Once daily for 16 weeks	5% L-ascorbic acid	--	Significant subjective improvement on HQ side, no significant difference in colorimetric measures	Irritation
								4% HQ	--		Irritation

TABLE 1. CONTINUED

Summary of Topical Treatments for Melasma											
Author	Design	No. of Patients†	Skin Type (Location)	Follow-up	Primary Outcome	Other Outcome Measures	Regimen	Treatment	Baseline‡	Results‡	Side Effects
Dioic Acid											
Tirado-Sanchez[52]	OL	96	III (Mexico)	12 weeks	MASI	None	Twice daily for 12 weeks	1% dioic acid	14.52 ± 3.4	6.05 ± 1.2*	Erythema, burning, pruritus, and acneiform reaction
								2% HQ	15.22 ± 2.4	6.34 ± 1.3*	Erythema, burning, pruritus, acneiform reaction
Ellagic acid and Arbutin											
Ertam[53]	OL	29	II-IV (Turkey)	6 months	Colorimetry using Mexameter®	None	Twice daily for 6 months	1% arbutin	--	Z = -2.803*	None
								1% synthetic ellagic acid	--	Z = -2.075*	None
								1% natural ellagic acid (plant extract)	--	Z = -2.803*	None
Flutamide											
Adalat-khah[54]	DB	73	Not reported (Iran)	4 months	MASI and colorimetry using Mexameter®	Patient satisfaction	Once daily for 4 months	1% flutamide	--	Significant improvement in MASI from baseline for both groups with superior efficacy for flutamide group; no significant difference in colorimetric measures between groups	Not reported
								4% HQ	--		Not reported

DB: double-blind, DITTS: Decreased Index of Total Target Score, EGF: epidermal growth factor, FA: fluocinolone acetonide, GAIS: Global Aesthetic Improvement Scale, GSS: Global Severity Score, HQ: hydroquinone, IGA: Investigator's Global Assessment, MASI: Melasma Area and Severity Index, mMASI: Modified Melasma Area and Severity Index, MelasQoL: Melasma Quality of Life scale, OL: open label, PC: placebo-controlled, PSA: Patient's Self-Assessment, RA: retinoic acid, SB: single-blind, SF: split-face, TXA: tranexamic acid, VC: vehicle-controlled. Asterisks (*) denotes significant improvement from baseline. Hash sign (#) denotes significant improvement compared to other treatment groups. †Sample size is based on per-protocol population (i.e., all patients who completed assigned treatment) unless otherwise specified. ‡Baseline values and results are based on primary outcome measure(s). §Sample size is based on intent-to-treat population (i.e., all patients who were randomized). ¶DITTS > 0.3 indicates Improvement[30]

TABLE 2.

Recommendations and Quality of Evidence				
Medication (# of RCTs)	**Strength of Recommendation**	**Quality of Evidence**	**Comparison to HQ**	**Notes**
Benefits outweigh risks and burden				
Azelaic acid (2)	Weak	Moderate	More effective in open-label RCT	Poorly designed RCTs.
Cysteamine (2)	Strong	Moderate	None	Reported to have anti-cancer effects. May lead to diffuse skin brightening. No long-term adverse event. May have unpleasant smell.
Epidermal growth factor (1)	Weak	Moderate	None	Small sample size.
Hydroquinone (liposomal-delivered) (1)	Weak	Moderate	Similar	Theoretical enhanced skin penetration.
Lignin Peroxidase (1)	Weak	Moderate	Similar efficacy and safety profile.	Small sample size.
Mulberry extract (1)	Weak	Moderate	None	Mild adverse event profile.
Niacinamide (1)	Weak	Moderate	Similar efficacy with milder adverse events.	Evaluated in one poorly powered study.
Rumex Occidentalis (1)	Weak	Moderate	None	Mild adverse event profile
Tranexamic acid (5)	Strong	High	Similar efficacy with fewer adverse events.	Theoretical risk for thrombosis.
Triple Combination (5)	Strong	High	Better efficacy with similar adverse event profile.	Risk of ochronosis and theoretical risk for carcinogenesis.
4-*n*-butylresorcinol (3)	Weak	High	None	Mild adverse events.
Benefits closely balanced with risks				
Glycolic acid (2)	Weak	Moderate	Only evaluated in combination with 4% HQ.	Increased risk of skin desquamation.
Kojic acid (2)	Weak	Moderate	Less effective as stand-alone.	May be combined with 4% HQ for increased efficacy.
Risks and burden outweigh benefits				
Parsley (1)	Weak	Moderate	Similar efficacy and adverse events	Formulation needs to be prepared by subjects, which increases burden of treatment.
Zinc sulfate (2)	Strong	High	Less effective	Risk for PIH.
Insufficient evidence to determine net benefit				
Aloe vera (1)	n/a	Moderate	None	No placebo or HQ comparison group. Used safely in pregnant patients.
Ascorbic Acid (1)	n/a	Moderate	Similar or worse efficacy	Ascorbic acid readily degrades and needs to be combined with other agents.
Dioic Acid (1)	n/a	Moderate	Similar efficacy	Acneiform reaction from oily vehicle.
Ellagic acid and arbutin (1)	n/a	Moderate	None	No placebo or HQ comparison group.
Flutamide (1)	n/a	Moderate	Similar efficacy	Adverse event profile was not provided. Risk of hormonal therapy not evaluated.

TABLE 3.

Mechanism of Action of Topical Agents	
Mechanism of Action	**Drug**
Tyrosinase inhibitor	Hydroquinone, Cysteamine, Kojic acid, Arbutin, Azelaic acid, Ascorbic acid, Ellagic acid, *Aloe vera, Rumex occidnetalis,* 4-*n*-butylresorcinol, Glycolic acid, EGF
Dopa oxidase inhibitor	Mulberry extract
Peroxidase substrates / inhibitors	Hydroquinone, Cysteamine
Increasing intracellular glutathione	Cysteamine
Nuclear PPAR receptor agonist	Dioic acid
Block plasmin pathway	Tranexamic acid
Prevent Melanosome transfer	Niacinamide, Tretinoin, Dioic acid
Anti-hormonal	Flutamide
Increase keratinocyte turnover	Tretinoin, Glycolic acid
Cytotoxic	Hydroquinone, Azelaic acid
Unknown	Zinc sulfate, Parsley, Lignin peroxidase

DISCUSSION

Herein, we provided evidence-based recommendations on the safety and efficacy of topical medications for melasma (Table 2). The topical agents are presented below in alphabetical order in categories according to their risk and benefit to patients with melasma. According to ACP guidelines, a strong recommendation may apply to most patients without reservations, whereas a weak recommendation differs according to an individual patient's circumstances. As only RCTs were reviewed, all recommendations were supported by moderate-quality (ie, one or more poorly designed RCT) or high quality of evidence (ie, one or more well designed RCT).

Multiple RCTs used 4% topical HQ as an active ingredient in combination therapies or comparison arms, but most of the literature on 4% HQ as a therapeutic modality was published before 2003. Cysteamine, TC, and TXA received the strongest recommendation of benefit. These medications had greater efficacy and/or milder AE profiles compared with topical HQ. A full description of topical treatments is provided below, and the mechanisms of action are provided in Table 3.

Benefits Outweigh Risks and Burden

Azelaic acid – weak recommendation

Two poorly designed RCTs examined the efficacy of azelaic acid. In an open-label study, 29 patients received twice daily 20% azelaic acid or 4% HQ for 8 weeks. 20% azelaic acid was more effective than 4% HQ according to the Melasma Area and Severity Index (MASI) score, but there is a significant bias in this study due to the open-label design.[11] The clinical photographs demonstrated good clinical responses for both treatment arms.

In another open-label RCT, patients received azelaic acid of various concentrations (5%, 10% and 20%) with 3 different supplemental formulations.[12] All 3 azelaic acid formulations improved colorimetric scores after 6 months of twice daily application. The most effective formulation contained 20% azelaic acid with 10% mandelic acid, 5% phytic acid, 5% 4-*n*-butyl resorcinol, and 2% ferulic acid (Sesderma, Valencia, Spain). No AE profile was provided. Azelaic acid received a weak recommendation due to the poor study design of the included articles. Both studies had an open-label study design and one study compared combination formulations without comparing individual ingredients. The 2 identified studies use different concentrations of azelaic acid (range 5% to 20%), which also confounds results.

Cysteamine – strong recommendation

Cysteamine is approved by the U.S. Food and Drug Administration for the treatment of cystinosis and has been shown to inhibit melanogenesis at high concentrations.[13,14] In 2 well-designed double-blind RCTs, 50 and 40 patients with melasma were treated with 5% cysteamine (Cysteamine®, Scientis Pharma SA, Geneva, Switzerland) or placebo daily for 4 months.[13,14] In both studies, cysteamine significantly reduced MASI scores compared with placebo. In the second study, significant colorimetric differences were found favoring topical cysteamine compared with the placebo at 2 months and 4 months, and the Investigator's Global Assessment (IGA) and patient feedback indicated positive efficacy of cysteamine. Patients reported erythema, dryness, itching, burning sensation, and irritation following cysteamine therapy. Side effects were associated with prolonged exposure to the topical agent, and removing the cysteamine by washing may decrease these side effects in patients. Clinical photos demonstrated diffuse skin brightening. Cysteamine has not been directly compared with 4% HQ.

Cysteamine is reported to have anti-cancer and anti-melanoma effects, which may be beneficial compared with HQ.[15,16] Cysteamine may lead to diffuse skin brightening, and some patients report an unpleasant odor from cysteamine. Cysteamine is widely used in Europe, but is not commercially available in the United States. As a stand-alone agent, cysteamine received a strong recommendation as it has a beneficial efficacy and safety profile.

Epidermal growth factor – weak recommendation

The topical application of EGF has been evaluated for the promotion of wound healing and prevention of post-inflammatory hyperpigmentation (PIH) after laser resurfacing of facial skin.[17] In one double-blind, split-face RCT, 50 patients were treated with topical EGF serum (DNARenewal, Beverly Hills, CA) vs placebo on each designated side of the face, twice daily for 8 weeks.[17] According to the Physician Global Aesthetic Improvement Scale,

there was an improvement in the melasma in 73.4% of patients on the EGF-treated side vs 13% on the placebo side. The average Melasma Quality of Life questionnaire score decreased from 42 to 33, with 73% of patients having an improvement in their score. No AEs were reported with use of either treatment.

While the authors concluded that topical EGF is a safe and effective treatment for melasma, additional RCTs with greater power and validated outcome measures are needed to evaluate the efficacy of topical EGF for melasma. Thus, topical EGF received a weak recommendation.

Hydroquinone (Liposomal) – weak recommendation
One double-blind RCT compared once daily treatment with 4% liposomal HQ (prepared by fusion method) to standard formulations of 4% HQ for 12 weeks, and demonstrated similar efficacy between the treatment regimens at week 4 following the end of the treatment course.[18] AEs for liposomal HQ were not reported. As a result, any added benefit of liposomal vehicle is minimal.

Lignin peroxidase – weak recommendation
One split-face RCT compared the efficacy of twice daily lignin peroxidase (elure, Syneron Medical Ltd, Yokneam, Israel) in two cohorts of 30 patients over 12 weeks.[19] In the first cohort, lignin peroxidase significantly improved MASI compared with no treatment. In the second cohort, there was no difference in MASI score between the lignin peroxidase and 4% HQ groups. Investigator grading indicated that lignin peroxidase resulted in improved skin texture. There were no AEs from either treatment. Lignin peroxidase improved patient melasma compared with no treatment.

Mulberry extract – weak recommendation
One single-blind RCT found that twice daily 75% mulberry extract oil for 8 weeks significantly improved patient MASI compared with placebo.[20] Clinical photographs were consistent and showed decreased pigmentation following mulberry extract treatment. Patients treated with mulberry extract reported fewer AEs than the control group. Mulberry extract received a weak recommendation, as additional research is needed to establish the efficacy of mulberry extract for periods greater than 8 weeks and compared with HQ.

Niacinamide – weak recommendation
Niacinamide, also known as vitamin B3, may decrease skin pigmentation by preventing melanosome transfer.[21] One double-blind, split-face RCT of 27 patients compared the efficacy of 4% niacinamide (Nicomide-T Cream 4%, DUSA Pharmaceuticals Inc, Wilmington, MA) with 4% HQ every 3 hours during the daytime for 8 weeks.[22] Both treatments reduced MASI significantly at week 8 compared with baseline. Niacinamide was associated with fewer and milder AEs. Colorimetric measures did not show statistical differences between both sides. However, according to the IGA, good to excellent improvement was observed with niacinamide in 44% of patients compared with 55% with HQ. Niacinamide received a weak recommendation, but there is promising efficacy from a single study.

Rumex occidentalis (Western Dock) – weak recommendation
One double-blind RCT compared the efficacy of twice daily 3% *Rumex occidentalis* (a perennial herb), 4% HQ, and placebo for 8 weeks in 45 patients.[23] The placebo had no significant effect, while the 3% *Rumex occidentalis* and 4% HQ significantly decreased MASI scores and colorimetric measures. Patients treated with *Rumex occidentalis* reported mild peeling. Clinical photographs demonstrated decreased pigmentation and diffuse skin brightening.[23] *Rumex occidentalis* reduced patient melasma and may be worthy of future research.

Tranexamic acid – strong recommendation
Five RCTs examined the use of topical TXA for patients with melasma. In one study of 60 patients, twice daily treatment with 6.5% TXA (Pazana Laboratory Asia Co., Ltd, Bangkok, Thailand) significantly improved melasma compared with vehicle at week 8.[24] Clinical photographs showed improvement following TXA treatment, but mild pre-treatment severity. However, in another double-blind, split-face RCT, 5% TXA performed no better than the vehicle.[25] Both treatment and control reduced melasma, but there was no difference in efficacy as determined by MASI and colorimetry. In a 60 patient double-blind study, 5% TXA vs 2% HQ twice daily both significantly decreased MASI.[26] 5% TXA was associated with higher patient satisfaction and less skin irritation.[26] In another split-face, double-blind study, 5% liposomal TXA (prepared by fusion method) had similar efficacy in reducing patient MASI score compared with 4% HQ after twice daily treatment for 12 weeks.[27] Skin irritation only occurred in the 4% HQ treated group.[27] In a split-face, double-blind study of twice daily 3% TXA vs 3% HQ and 0.01% dexamethasone, both treatments significantly reduced MASI scores.[28] Photographs showed decreased pigmentation. There was no difference in treatment efficacy between groups, but topical application of 3% HQ and 0.01% dexamethasone was associated with an increased incidence of AEs.[28]

TXA had similar efficacy to HQ with a milder AE profile and received a strong recommendation. The efficacy of TXA is dependent on concentration dose when used as monotherapy. TXA is a lysine analogue and carries a theoretical risk for thrombosis due to the anti-fibrinolytic effects. However, no evidence of increased clotting in low-risk patients was found in a recently published review of the safety and efficacy of oral TXA for melasma.[29] Topical TXA likely has decreased vasculature circulation compared with oral administration, but the theoretical risk of blood clots remains. Clinicians may consider topical TXA as an alternative to HQ in patients without predispositions to thrombotic events.

Triple combination therapy – strong recommendation

Five RCTs have examined the efficacy of TC agents. One 211 patient double-blind RCT found that 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide (FA) (Zhejiang Rishengchang Pharmaceutical Co., Ltd, Zhejiang, China) was more effective than placebo at clearing melasma based on the decreased index of total target score.[30] Another double-blind RCT of 32 patients found that daily 4% HQ, 0.05% tretinoin, and 0.05% dexamethasone had better investigator-rated outcomes than 4% HQ after 12 weeks.[31] Erythema and scaling were more prevalent following TC therapy (87.5% vs 43.7%). An open-label RCT of 119 patients found that once daily TC cream of 4% HQ, 0.05% tretinoin, and 0.01% FA (Tri-Luma®, Galderma, Lausanne, Switzerland) more effectively cleared melasma compared with twice daily 4% HQ, with 35% of patients achieving complete clearance on TC therapy compared with 5.1% in the HQ group.[32] A 242 patient single-blind study evaluating the same treatment regimen similarly demonstrated reduced MASI score compared with 4% HQ.[33] Patient photographs were consistent and showed improvement of melasma.[33] In a single-blind 641 patient RCT, a TC hydrophilic cream containing 4% HQ, 0.05% tretinoin, and 0.01% FA more effectively cleared melasma compared with dual combination regimens of tretinoin plus HQ, tretinoin plus FA, or HQ plus FA.[34] AEs of erythema, skin peeling, burning, and stinging sensation were mild and similar among all treatment arms.[34]

TC therapy was superior to 4% HQ with a similar AE profile and received a strong recommendation. TC therapies demonstrate the benefit of synergistic treatments in which HQ decreases melanogenesis, tretinoin increases keratinocyte turnover, and steroids reduce inflammation. Evidence from epidemiological studies and case reports has not revealed an increased risk of cancer but clinicians may consider limiting chronic exposure.[9] If clinical goals have been achieved, a maintenance regimen of once or twice weekly TC therapy may minimize the risk for ochronosis.[35,36] Relapse has been shown to occur in 50% of patients approximately 190 days following the establishment of a maintenance regimen compared with 58 days following abrupt cessation of therapy.[35-37] For patients seeking a non-HQ therapeutic approach for the treatment of melasma due to HQ associated safety profile, we recommend against TC.

4-n-butylresorcinol – weak recommendation

Three double-blind, split-face RCTs compared the efficacy of 4-*n*-butylresorcinol 0.1% cream or 0.3% serum with vehicle.[38-40] In all 3 studies, 4-*n*-butylresorcinol significantly reduced skin pigmentation compared with vehicle based on colorimetric measures and clinical pigmentation score. In one study, the depigmenting effects of 4-*n*-butylresorcinol 0.3% serum increased until week 8 and then plateaued.[40] The other two studies only compared the efficacy until week 8. Adverse events were mild in all three studies. Photographs showed improvement following 4-*n*-butylresorcinol topical therapies.[38-40]

4-*n*-butylresorcinol decreased skin pigmentation and may be a useful as a short-term treatment for melasma, but the long-term efficacy beyond 12 weeks is unclear. In vitro studies have indicated that 4-*n*-butylresorcinol was the most potent inhibitor of tyrosinase compared with HQ, arbutin, and kojic acid.[41] 4-*n*-butylresorcinol received a weak recommendation, as additional studies are needed to compare the efficacy of 4-*n*-butylresorcinol to establish the duration of effect greater than 8 to 12 weeks, and comparison studies to 4% HQ may provide additional strength of data.

Benefits Closely Balanced With Risks and Burden

Glycolic acid – weak recommendation

Glycolic acid is believed to improve melasma by accelerating desquamation.[42] Two RCTs examined the efficacy of combination 10% glycolic acid and 4% HQ for melasma.[43,44] In a vehicle-controlled, double-blind RCT of 35 patients, twice daily application of a cream containing 10% buffered glycolic acid with 4% HQ, ascorbic acid, vitamin E, and sunscreen (Glyquin, ICN Pharmaceuticals, Costa Mesa, CA) was applied for 12 weeks.[43] The combination 10% glycolic acid product significantly improved melasma compared with sunscreen-only control as determined by MASI and colorimetry.[43] Another single-blind RCT compared daily 4% HQ alone with 4% HQ with 0.01% hyaluronic acid; 4% HQ with 10% glycolic acid; 4% HQ with 0.01% hyaluronic and 10% glycolic acid; or placebo.[44] All 4 topical treatments improved melasma from baseline. The most significant decrease in melasma was measured following 4% HQ with 0.01% hyaluronic acid and 10% glycolic acid. Topical 4% HQ with supplemental glycolic acid was more irritating to skin than HQ alone. Post-treatment photographs showed localized skin brightening around the treatment site.

Glycolic acid is weakly recommended as a supplement to 4% HQ, as the benefits and risk of skin desquamation should be carefully considered for each patient. Additionally, the RCTs do not directly compare the efficacy of glycolic acid alone with HQ alone. Glycolic acid supplementation had greater efficacy and more severe AEs compared with 4% HQ alone. Skin desquamation from glycolic acid may be minimized if patients apply a moisturizing cream concurrently.[9] Glycolic acid appears best suited as adjunct therapy for melasma and not a primary, first-line approach.

Kojic acid – weak recommendation

Kojic acid is a tyrosinase inhibitor produced by several fungi species. Two poorly designed RCTs examined the use of kojic acid for melasma. In an 80-patient single-blind RCT, 4 different formulations of 1% kojic acid alone or in combination with 2% HQ and/or 0.1% betamethasone were tested.[45] All 4 treatment groups significantly reduced MASI score after daily treatment for 12 weeks.[45] The authors did not statistically compare inter-treatment efficacy but concluded that 1% kojic acid with 2% HQ

had the best efficacy and 1% kojic acid with 0.1% betamethasone was the least effective. 1% kojic acid, 2% HQ, and 0.1% betamethasone was associated with acneiform eruptions. In another RCT, daily 0.75% kojic acid with 2.5% ascorbic acid for 12 weeks was inferior to 4% HQ.[46] Photographs demonstrated minimal efficacy for kojic acid as a stand-alone treatment. Anecdotal clinical evidence suggests that compounding 12% HQ with 6% kojic acid may be an effective treatment not associated with diffuse skin brightening, but this formulation has not been studied in an RCT. Based upon the available published literature reviewed, kojic acid received a weak recommendation when combined with other agents, and evidence does not support recommendation as a stand-alone treatment for melasma.

Risks and Burden Outweigh Benefits

Parsley – weak recommendation

In a poorly designed double-blind RCT, patients applied parsley or 4% HQ daily for 8 weeks.[47] The patients in the parsley group had to self-brew 2.5 g of parsley in 125 ml of water. Both treatments significantly improved MASI from baseline. AEs in the parsley and 4% HQ group included irritation, redness, and itching. As patients were required to self-prepare parsley extract to prevent treatment expiration, the use of parsley was weakly recommended. Additionally, differences in sample preparation may lead to variability in treatment results.

Zinc sulfate – strong recommendation

Zinc sulfate has been used to treat numerous skin conditions including acne vulgaris and warts. Two RCTs examined the use of once or twice daily 10% zinc sulfate for melasma.[48,49] In both studies, topical application of 10% zinc sulfate reduced MASI score less effectively than 4% HQ. One study noted that patients treated with 4% HQ alone complained of greater skin irritation. However, 10% zinc sulfate resulted in PIH in 2 patients that resolved with topical tretinoin treatment.[49] As zinc sulfate was inferior to 4% HQ and carried a risk of PIH, we strongly do not recommend zinc sulfate for the treatment of melasma.

Insufficient Evidence to Determine Net Benefit

Aloe vera – no strength of recommendation

One double-blind study compared the efficacy of 2 aloe vera formulations (0.5% gel extract or 0.25% liposome-encapsulated gel extract) in 180 pregnant patients with pre-existing melasma.[50] After 5 weeks, liposome-encapsulated aloe vera significantly improved patient MASI compared with the standard gel formulation. As there was no placebo or HQ control group, it is difficult to determine the relative efficacy of aloe vera. However, the net risk of AEs is likely low as the treatment was used in pregnant patients. The study did not describe the frequency of aloe vera application.

Ascorbic acid – no strength of recommendation

In a 16 patient, split-face, double-blind RCT, patients were less satisfied with 5% L-ascorbic acid (La Roche-Posay, France) compared with 4% HQ after 16 weeks.[51] Colorimetric analysis demonstrated no difference between treatment arms, and HQ was more irritating to the skin. Ascorbic acid is readily oxidized, which limits its use as a stand-alone treatment but may be combined with other topical agents.[9]

Dioic acid – no strength of recommendation

One open-label RCT of 96 patients compared twice daily 1% dioic acid with 2% HQ for 12 weeks. 1% dioic acid and 2% HQ improved MASI scores from baseline, but there was no significant difference between dioic acid and HQ.[52] Patients treated with dioic acid had a higher incidence of acneiform reaction, which the authors attributed to an oily vehicle. An open-label design limited the strength of this study.

Ellagic acid and arbutin – no strength of recommendation

In an open-label RCT involving 29 patients, twice daily treatment with 1% synthetic ellagic acid, 1% arbutin, or plant extract with 1% natural ellagic acid significantly improved skin pigmentation after 6 months without the occurrence of AEs.[53] Limitations in the study design included the lack of blinding and lack of a placebo-control. Thus, additional research is needed before conclusions can be drawn about ellagic acid and arbutin therapy for melasma.

Flutamide – no strength of recommendation

One double-blind study compared the efficacy of daily topical 1% flutamide, an anti-androgenic drug, with 4% HQ over 4 months.[54] Both treatments reduced MASI compared with baseline. Flutamide was more effective than HQ according to MASI and patient satisfaction but there was no difference between treatments when assessed using colorimetric analysis. The AE profile was not provided, and the safety of hormonal therapy should be evaluated before a recommendation can be made.

LIMITATIONS

Currently, there is no universally effective treatment for melasma, and some established topical agents carry significant safety risks that may reduce patient compliance and satisfaction. Topical HQ, the basis for many combination therapies, may be less effective in patients with darker skin phenotypes and is associated with ochronosis.[9,55] Other novel agents have shown promising results, but are limited by small sample sizes, poor study design, and limited high quality published RCTs. When evaluating naturally-derived or compounded topical therapies, it is essential to consider the reproducibility of the chemical composition. Differences in treatment concentration or secondary ingredients may have a significant impact on therapeutic efficacy. Additionally, several RCTs used natural agents published in non-English languages. These studies may have added to the literature, but we were unable to evaluate these studies.

CONCLUSION

We performed a systematic review of topical treatments for melasma. Strong evidence-based recommendations include cysteamine, TC, and TXA as first-line treatments for melasma. Cysteamine has excellent efficacy, is reported to have anti-cancer properties, and has no known risk for thrombosis or ochronosis. TC therapies and TXA are effective for melasma but carry theoretical risks for ochronosis or thrombosis, respectively. Natural compounds are associated with low risk for AEs, but more research is needed to determine the efficacy, optimal formulation, and appropriate concentration of novel treatments.

For all topical agents, continued treatment and use of medications is necessary as pigmentation may recur following treatment cessation. Future large RCTs with control arms using standard-of-care treatments (ie, HQ or TC) are necessary to assess the relative risks and benefits of a novel agent. Current topical treatments mostly inhibit melanin formation and transfer, but do not target the vascular components of melasma, inflammation, or underlying disease etiology. We believe that synergetic combination approaches are likely to have greater efficacy than stand-alone treatments. Future mechanistic research on the underlying etiology of melasma may facilitate the development of targeted approaches.

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DISCLOSURES

Dr. Jagdeo is a speaker for L'Oréal/Skinceuticals and a consultant for Scientis. Dr. Jagdeo is on the scientific advisory board for Sun Pharma/DUSA Pharmaceuticals, Inc. for the product Levulan® photodynamic therapy. No funding has been received for this article. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the U.S. Department of Veterans Affairs or the United States Government.

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