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Efficacy and Safety of *Centella Asiatica* (*L.*) Urb. on Wrinkles: A Systematic Review of Published Data and Network Meta-Analysis

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Synopsis

Centella asiatica has many applications in cosmetics, including wrinkle treatments, but its effectiveness remains to be clarified. This systematic review study aimed to demonstrate the efficacy and safety of *C. asiatica* for reducing facial wrinkles. PubMed, Excerpta Medica dataBASE (EMBASE), Cochrane Central Register of clinical trials, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Thai Library Integrated System, and Thai university database/journals were searched until May 2019. Five double-blinded randomised controlled trials, including 172 Asian females, were included. Endpoints were wrinkling measured by visual score, image analysis, and participant satisfaction. Two placebo-controlled studies applied gel/creams containing *C. asiatica* or asiaticoside for 12 w to periorbital skin. Two studies applied tretinoin or *Pueraria mirifica* contralaterally and by network meta-analysis *C. asiatica* appeared more effective than *P. mirifica* but possibly less than tretinoin. Asiaticoside applied as a lipstick for 8 w reduced lip wrinkling. Skin hydration was markedly raised by *C. asiatica* but not tretinoin. One study reported 10 adverse events for *C. asiatica* and 35 for tretinoin. Cochrane risk of bias was generally low, reporting was weak, and lack of *C. asiatica* standardization prevents general application. From the reported data, it is possible to conclude that *C. asiatica* improved lip and periocular wrinkles, and may replace retinoids if its long-term safety is established and *C. asiatica* is standardized.

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INTRODUCTION

Cutaneous wrinkling is commonly associated with aging, mechanical and chemical insults, and radiation. The reduced skin thickness and resilience arise from the failure of fibroblast reconstruction of the dermal extracellular matrix (1). To date, the most effective and commonly used treatments are topical retinoids that bind to their nuclear receptors, thereby increasing collagen I and III production, and reducing inflammation among other actions (2). But these compounds have side effects, a narrow therapeutic window, and are available only on prescription in some countries, a barrier to cosmetic applications.

Several herbal preparations have been reported to curtail or reverse wrinkle formation, including *Centella asiatica. Centella asiatica* (*L.*) Urban (Apiaceae), commonly called Asiatic pennywort, Gotu kola, or Indian pennywort,is a leafy rampant creeper that grows predominantly in wetlands across southern and eastern Asia. Its leaves in particular are used as food in varying forms while also enjoying widespread application in medicines to treat a diverse range of ailments (3). These include peptic ulcer (4), diarrhea (5), flatulence (5), convulsions (6), and cognitive impairment (7). For cosmetic purposes, *C. asiatica* has been reported to ameliorate bruising, to retard loss of skin elasticity (8,9), to improve postpartum stretch marks (10), to reduce skin wrinkling (11), and to promote wound healing (12). The active ingredients of *C. asiatica* are several pentacyclic triterpenoids and their glycosides including asiatic acid, asiaticoside, madecassic acid, and madecassoside which collectively comprise 2–8% dry weight of the plant (13) and are responsible for the medicinal actions (3) of cosmetics (14). Lesser amounts of other terpenes and many secondary metabolites are found in *C. asiatica* but too little for pharmacological action *C. asiatica. C. asiatica* has been added to numerous formulations for the aforementioned conditions which are described in several reviews about *C. asiatica*, but there is a paucity of those focusing on the efficacy and safety data when present in cosmetics. This study aimed to address this issue, specifically by systematically reviewing studies on facial wrinkles.

METHODS

ELIGIBILITY CRITERIA

This systematic review and network meta-analysis (NMA) used characteristics following the participants, interventions, comparisons, outcomes, study design criteria: the participants were healthy volunteers; the intervention groups received *C. asiatica* as the sole active ingredient, and applied topically; the comparator groups did not receive *C. asiatica*; outcome measures were (i) skin wrinkling, (ii) adverse events (AEs), or (iii) participant opinion/satisfaction; and the study design was randomized controlled trials (RCTs).

SEARCH STRATEGY

We searched PubMed, Embase, the Cochrane Central Register of clinical trials, Allied and Complementary Medicine Database, CINAHL, the Thai Library Integrated System, and Thai university databases/journals (Chulalongkorn, Mahidol, and Naresuan Universities), and also screened the WHO clinical trials registry, Clinicaltrials.gov, "grey" literature

reports and similar studies from their inception to May 2019. Search keywords were "*C. asiatica*," "Gotu kola," "Asiatic pennywort," and "Indian pennywort."

We included studies that assessed cosmetic efficacy and safety by (a) RCTs that compared *C. asiatica* with no *C. asiatica*; (b) RCTs having sufficient information about cosmetic outcomes classified as (i) skin wrinkling, (ii) AEs, or (iii) participant opinion/satisfaction; and (c) being published in any language.

Two discovered studies were unpublished masters thesis lodged in the Thai thesis database. We also searched national databases in India and Malaysia, but no study fitted our criteria.

DATA EXTRACTION

Two investigators (N. C. and P. M.) independently screened the titles and abstracts of relevant studies and made full-text assessments of those written by the same authors following our eligibility criteria. We extracted by study design, area of use, participant characteristics (such as gender, mean age, and number of participants), details of the intervention (such as dosage regimens, dose, and durations), and cosmetic outcomes. All extracted data were independently checked by C. K. and C. N. S.

QUALITY ASSESSMENT

Each included study was assessed by three investigators (C. K., P. M., and C. N. S.) using the Cochrane Risk of bias 2.0 tool for RCTs (15).

DATA ANALYSIS

For each cosmetic outcome, the mean differences (MD) between *C. asiatica* and comparator groups [and 95% confidence intervals (CIs)] after 0, 4, 8, and 12 w using *C. asiatica*. Intergroup comparisons were performed using the DerSimonian–Laird random effects model (16). Heterogeneity in each comparison was assessed using the I^2 statistic (17). Statistical analysis was performed using STATA/SE, v. 14 (StataCorp LLC, College Station, TX).

RESULT

SEARCH RESULTS

Six hundred seventy-one articles were identified. After screening, 654 articles were excluded because they did not fit the eligibility criteria, and 12 articles described the same studies, leaving five included articles (Figure 1).

STUDY CHARACTERISTICS

Two studies were from South Korea and two from Thailand (in Thai) and one from China (*C. asiatica* has been tested in many Italian trials but excluded because the intervention

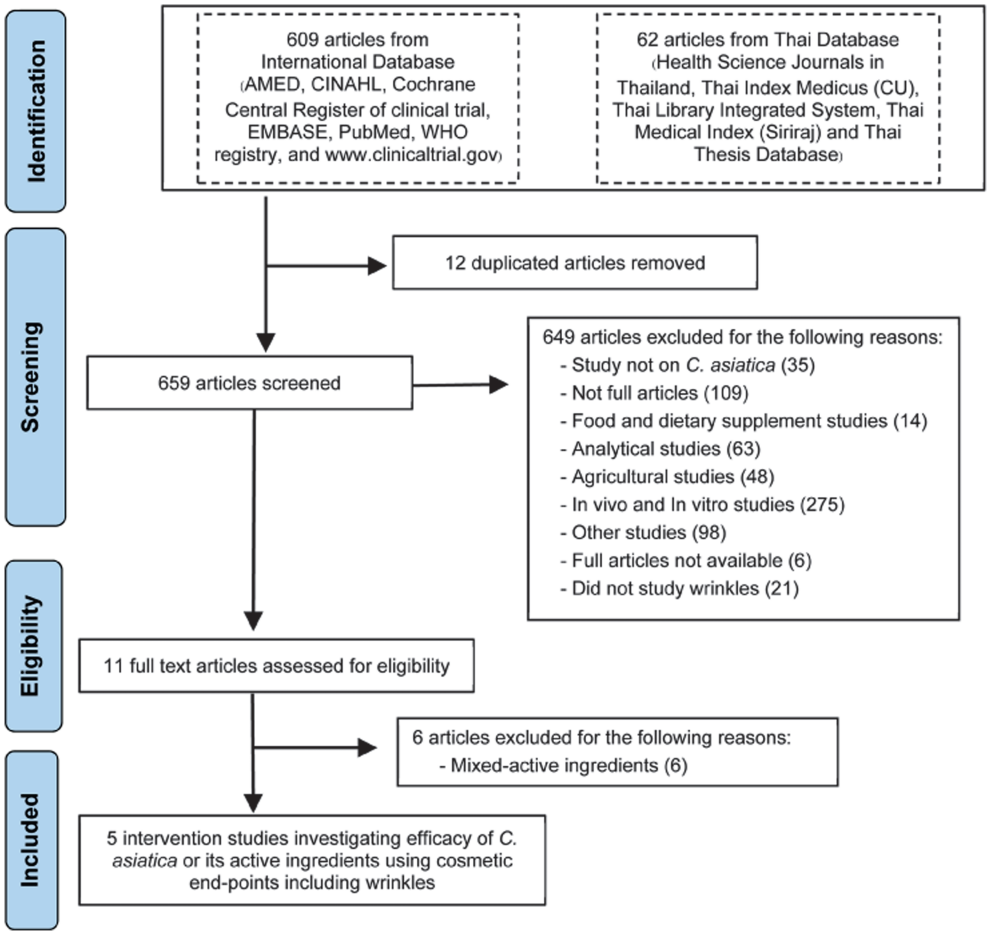

Figure 1. Flow of included studies.

contained additional active ingredients). The published results considered in our systematic review included 172 participants in the five studies (18–22) (Table I). All the studies were RCTs that were double-blinded to treatment. Four studies were single groups using "split" protocols for both test and comparator treatments in the same participants. All participants were female of mean age 33.4 years. Three dosage forms were used [two studies used a cream (20–22), two used gels (18,19), and one study used a lipstick (19)]. Two cosmetic outcomes were identified: four studied periorbital wrinkles (three beneath the eyes and four lateral angle) and one lip wrinkles (19). Two studies were unpublished masters thesis lodged in the Thai thesis database, whereas the remainder were full journal articles.

QUALITY OF INCLUDED STUDIES

For study quality, the risk of biases was mostly low (Table II), but two studies had "some concerns" due to potential bias from unclear randomization. In addition, Lee et al. (18) and Zhang et al. (22) had incomplete data reporting, making it difficult to quantitate conclusions.

Table I
Characteristics of the Included Studies

Author	Gender (%)	Mean age, y	Number of samples (intervention: control)	Area	Type of control	Details of treatment			Details of outcome		
						Treatment regimen	Treatment detail	Duration, w	Outcome target	Measurement tool	Point of measure (at w)
Ryu et al. (19)	Female (100)	23.3	20–50 (25:25)	Lip	Placebo	0.2% asiaticoside lipstick	Apply twice daily	8	Wrinkle color	Five-point visual scoring scale Image analysis	0,4,8
Lee et al. (18)	Female (100)	46.6	27 (27:27)	Periorbital	Vehicle	0.1% asiaticoside cream	Apply twice daily	12	Wrinkle	Visiometer SV 600	0,4,8,12
Tangsumroengwong (20)	Female (100)	32	35 (35:35)	Periorbital	0.02% tretinoin gel	5% CA[a] extract gel	0.25 g at bedtime	12	Wrinkle Moisture Satisfaction AE	Visioscan VC98 RG5VSS Corneometer	0,4,8,12
Tongsrikeaw (21)	Female (100)	41.4	25 (25:25)	Peri-orbital	5% *Pueraria mirifica* gel	5% CA[a] extract gel	Apply twice daily	12	Wrinkle Satisfaction AE	Visioscan VC98 RG5VSS	0,4,8,12
Zhang et al. (22)	Female (100)	19–71	35	Lateral angle	Vehicle	*Centella* triterpenes cream®	Applied 3x daily	12	Periorbital wrinkling	Visioscan VC98 and dermatologist scoring	0,4,8,12

CA: *C. asiatica*, FTU: fingertip unit (5 mm. of cream from the tip of the index finger to the first top joint of the index finger). This study defined 1 FTU = 0.5 g. of cream.

[a]CA extract was ordered for Chang Kaew Natural Company, Nontaburi, Thailand, containing deionised water 88.25%, allantoin 0.3, glycerine 1.0, propylene glycol 2.0, carbopol 940 0.4, triethanolamine 0.4, aloe vera extract 1.0, cucumber extract 1.0, *Centella* extract 5.0, Glydant plus 0.2, Emulsogen HCO 040 0.45, shower fragrance, and green coloring. No description of how *Centella* extract was produced or standardized.

Table II
Quality Assessment of Included Studies Using the Cochrane Risk of bias v. 2.0 tool

Author	Bias from randomization	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Ryu et al. (19)	Some concern	Low	Low	Low	Low	Some concern
Lee et al. (18)	Low	Low	Low	Low	Low	Low
Tangsumroengwong (20)	Low	Low	Low	Low	Low	Low
Tongsrikeaw (21)	Low	Low	Low	Low	Low	Low
Zhang et al. (22)	Some concern	Low	Low	Low	Low	Some concern

Lee et al. (18) provided detailed numerical "roughness" data, but relation to wrinkle parameters was unclear. They measured six skin parameters determined by dermatologists which were bundled along with participant self-assessment into a single overall score. Some parameters were described as statistically significant, but effect sizes were not reported. In general, the quality and depth of reporting were poor.

INTERVENTIONS

Treatments were randomly allocated to either test or placebo/comparator. Three studies applied treatments twice daily, once a day, or thrice daily (Table I). Measurements were made at 4-w intervals beginning at baseline and continuing to 12 w, except Ryu et al. (19) who stopped at 8 w. Two studies (18,19) used 0.1 or 0.2% asiaticoside in their treatments. *C. asiatica* extract was the intervention in the other three studies but did not identify the plant source, strain, growing condition, detail the extraction method nor any standardization for likely active ingredients. All the studies were double blinded and controlled using a comparator similarly formulated to the intervention. Comparators were 0.02% tretinoin (20) or *Pueraria mirifica* extract (21) or placebo.

MOISTURISING SKIN

This was measured as capacitive impedance of ~20 μm of the corneum read as resonant frequency. *C. asiatica* gel increase mean moisture value of periorbital wrinkled skin by 26% between baseline and w 12 compared 1% with tretinoin and 12% and −1% for lateral canthus (Table III) (20).

LIP WRINKLES

A lipstick containing asiaticoside was applied to the lips for 8 w after which visual grading and image analysis of silicon casts showed reduced wrinkling by ~20%. As the depth

Table III
Outcomes of Studies

Study	Parameters measured	Method	Measurement method	Skin area studied	Time, w	*C. asiatica* product	Placebo/ comparator	*p*-value*	AEs/dropouts
Lee et al. (18)	Roughness corresponding to wrinkles	Silicon casts	Roughness by mage analysis	Periorbital skin (lateral to lateral canthus)	0	0.19 ± 0.01	0.20 ± 0.01	ns	NR
					4	0.20 ± 0.0	0.20 ± 0.01	ns	
					8	0.17 ± 0.01	0.18 ± 0.01	ns	
					12	0.15 ± 0.00	0.17 ± 0.00	<0.05	
	Hydration, roughness, laxity, suppleness, fine/ coarse wrinkles	Dermatologist visual grading	Bundled score	Periorbital skin (lateral to lateral canthus)	0	6.7**		<0.05	
					4	5.0			
			Presumed range 0–17		8	4.5			
					12	4.2			
	Self-assessment of participants					No quantitative data reported			
Ryu et al. (19)	Lip visual wrinkle scores	Photographs	Three dermatologist score 1–5	Lips	0	3.1 ± 1.0	3.0 ± 1.0	ns	AEs, NR
					4	2.9 ± 1.0	3.0 ± 1.0	ns	Two dropouts
					8	1.8 ± 0.9	2.3 ± 1.0	<0.05	Reason NR
	Analysis of silicon lip casts	Photographs	Image analysis of shadows	Lips	4	1.58 ± 18.4	−3.0 ± 24.5	ns	
					8	22.3 ± 20.3	3.5 ± 14.7	<0.01	
	Periorbital wrinkling	Spread of lipstick	Visual	Lip margines	8	0.32 ± 0.08	0.62 ± 0.15	<0.05	
	Colour depth of lips	Hue	Colorimetric (hue saturation index)	Lips	8	10.5 ± 2.0	17.3 ± 3.2	<0.05	

Table III
Continued

Study	Parameters measured	Method	Measurement method	Skin area studied	Time, w	*C. asiatica* product	Placebo/ comparator	*p*-value*	AEs/dropouts
	Wrinkles	Digital camera Samsung NX100	Rao-goldman Five point visual Scoring Scale	15 mm below lower eyelid	0	3.19 ± 0.53	3.28 ± 0.58	0.5	48-h forearm patch test
					4	3.19 ± 0.53	3.28 ± 0.58	0.5	
					8	3.06 ± 0.61	3.16 ± 0.67	0.5	No reactions
					12	2.91 ± 0.64	2.91 ± 0.53	0.9	
				15 mm lateral from lateral canthus	0	3.38 ± 0.61	3.38 ± 0.60	1.00	CAext =10
					4	3.38 ± 0.61	3.38 ± 0.61	1.00	
					8	3.22 ± 0.66	3.16 ± 0.62	0.67	Tretinoin = 35 rash, scaling, burning
					12	3.13 ± 0.71	3.06 ± 0.71	0.72	
		Visioscan VC98	Skin wrinkle	15 mm below lower eyelid	0	50.5 ± 5.1	50.7 ± 5.3	0.92	Three dropouts reason NR
					4	50.4 ± 5.0	50.7 ± 5.2	0.90	
					8	49.2 ± 5.3	49.8 ± 5.4	0.53	
					12	48.0 ± 5.0	48.0 ± 5.1	0.94	
Tangsumroengwongwong (20)				15 mm lateral from lateral canthus	0	53.3 ± 4.8	53.5 ± 4.4	0.7	
					4	53.3 ± 4.9	53.5 ± 4.5	0.9	
					8	51.9 ± 4.4	52.0 ± 4.3	0.9	
					12	51.0 ± 4.7	51.1 ± 4.6	0.7	
	Moisture	Corneometer	Skin resonant frequency, kHz	15 mm below lower eyelid	0	47.2 ± 3.2	45.2 ± 3.7	0.05	
					4	52.1 ± 2.9	45.2 ± 3.7	<0.001	
					8	56.1 ± 3.1	45.6 ± 3.8	<0.001	
					12	59.7 ± 3.8	45.6 ± 3.7	<0.001	
				15 mm lateral from lateral canthus	0	47.2 ± 4.3	47.0 ± 4.6	0.9	
					4	49.5 ± 3.9	46.7 ± 4.7	0.003	
					8	51.2 ± 3.7	46.7 ± 4.9	<0.001	
					12	53.1 ± 3.7	46.7 ± 4.9	<0.001	
	Satisfaction				12	No quantitative data			
	AEs	Visual observation	Scarlet, dry peeling skin, or stinging skin	Either site	4	*N* = 5	*N* = 18		
					8	*N* = 3	*N* = 12		
					12	*N* = 2	N = 5		

Table III
Continued

Study	Parameters measured	Method	Measurement method	Skin area studied	Time, w	*C. asiatica* product	Placebo/ comparator	*p*-value*	AEs/dropouts
Tongsrikeaw (21)	Wrinkle	Digital camera	Rao-goldman	15 mm lateral from lateral canthus	0	3.48 ± 0.55	3.48 ± 0.55	ns	0
					4	3.48 ± 0.55	3.48 ± 0.55	ns	
			Five-point visual score		8	3.42 ± 0.55	3.44 ± 0.54	0.7	
					12	3.38 ± 0.53	3.42 ± 0.54	0.5	Measured at w 12
				15 mm below lower eyelid	0	3.36 ± 0.55	3.36 ± 0.55	NS	
					4	3.36 ± 0.55	3.36 ± 0.55	NS	
					8	3.32 ± 0.55	3.34 ± 0.54	0.6	
					12	3.30 ± 0.54	3.32 ± 0.54	0.6	
		Visioscan VC98	Skin wrinkles	15 mm lateral from lateral canthus	0	58.6 ± 6.6	58.3 ± 6.0	0.6	
					4	56.8 ± 5.9	56.6 ± 5.9	0.7	
					8	54.1 ± 5.9	53.9 ± 5.9	0.7	
					12	51.9 ± 5.9	51.4 ± 6.2	0.5	
				15 mm below lower eyelid	0	56.2 ± 7.1	54.9 ± 6.9	0.1	
					4	54.1.±6.9	53.3 ± 6.7	0.2	
					8	50.2 ± 6.2	49.7 ± 6.7	0.002	
					12	47.1 ± 5.6	46.6 ± 6.6	0.5	
	Satisfaction	Patient satisfaction questionnaire	Patient satisfaction score	15 mm from lateral canthus. 15 mm below lower eyelid	12	3.52 ± 1.05	3.36 ± 0.99	NA	
	AEs	Visual observation		Either site	4	No AE	No AE		
					8	No AE	No AE		
					12	No AE	No AE		

Table III
Continued

Study	Parameters measured	Method	Measurement method	Skin area studied	Time, w	*C. asiatica* product	Placebo/ comparator	*p*-value*	AEs/dropouts
Zhang et al. (22)	Periorbital wrinkles	Photos assessed by nine dermatologists	10-point scale	Crow's feet	0	3.4 ± 1.5	3.3 ± 1.4		
					4	3.0 ± 1.5	3.3 ± 1.4	0.02	
					8	2.6 ± 1.2	3.2 ± 1.3	0.001	One dropout work-related cause
					12	2.5 ± 1.2	3.3 ± 1.4	0.001	AEs, NR
		Visioscan VC98	SEw-value	Crow's feet	12	Increased	decreased	<0.05	
		Self-assess-ment	Coarse and fine wrinkles	Crow's feet	12	Only fine wrinkles improved		<0.05	

*p-values compare intervention with placebo/comparator.
**Lee et al., not clear what these numbers mean (see comments in the article).

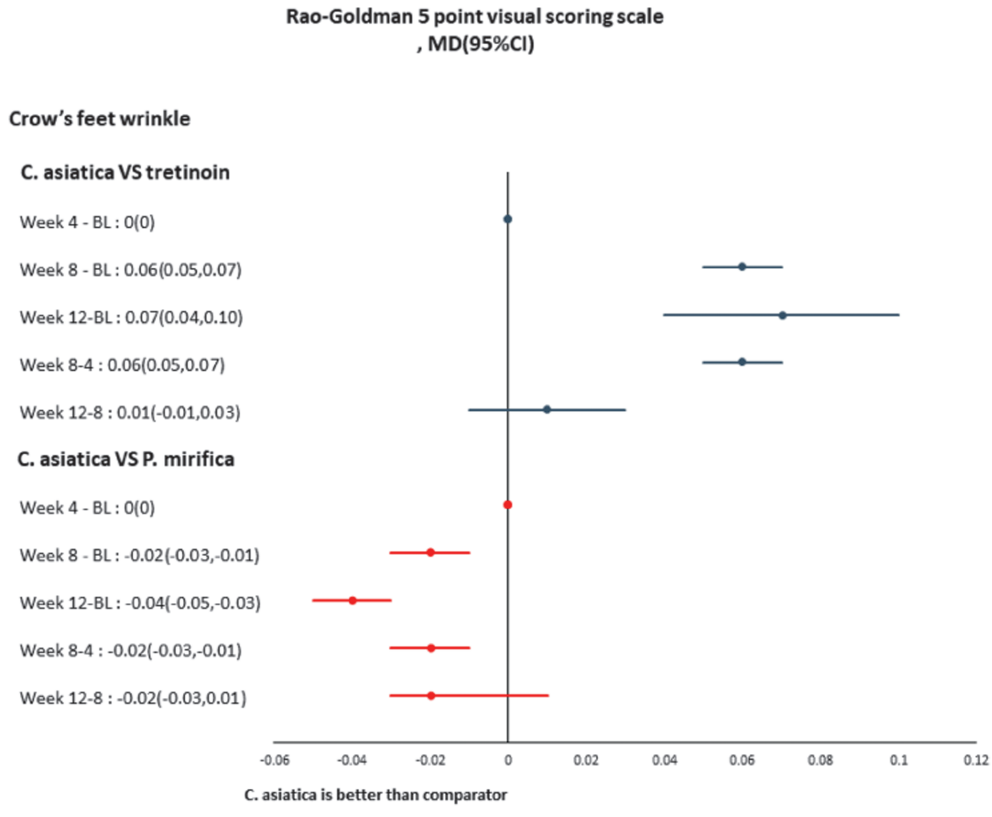

Figure 2. Lateral angle (crow's feet) wrinkles measured by the RG5VSS.

and number of wrinkles were reduced, the lipstick "bleeding" also improved significantly (Table III).

PERIOCULAR WRINKLES

We performed NMA on the three studies that compared *C. asiatica* with placebo. Periocular wrinkles below the eye and lateral canthal rhytids (crow's feet) were assessed using the Rao–Goldman five-point visual scoring scale (RG5VSS) and cutaneous topography using Visioscan imaging. *C. asiatica* reduced the MD measured by RG5VSS in crow's feet wrinkles compared with *P. mirifica* at w 8 and 12 by 0.02 (95% CI: −0.03, −0.01) and 0.04 (95% CI: −0.05, −0.03), respectively (Figure 2). *C. asiatica* reduced MD measured by RG5VSS in under eye wrinkles compared with *P. mirifica* at w 8 and 12 by 0.02 (95% CI: −0.02, −0.01) and 0.02 (95% CI: −0.04, −0.001), respectively (Figure 3). *C. asiatica* reduced MD measured by Visioscan in crow's feet wrinkles comparing *vehicle* at w 4, 8, and 12 by 0.4 (95% CI: −0.4, −0.4), 0.7 (95% CI: −0.77, −0.63), and 0.9 (95% CI: −0.97, −0.83), respectively (Figure 4). *C. asiatica* reduced MD measured by Visioscan in under eye wrinkle at w 4 and 8 compared with tretinoin by 0.04 (95% CI: −0.06, −0.02) and 0.3 (95% CI: −0.36, −0.24), respectively. When comparing *P. mirifica* at w 4 and 12 *C. asiatica* reduced MD by 0.46 (95% CI: −0.54, −0.38) and 0.84 (95% CI: −1.26, −0.42), respectively (Figure 5).

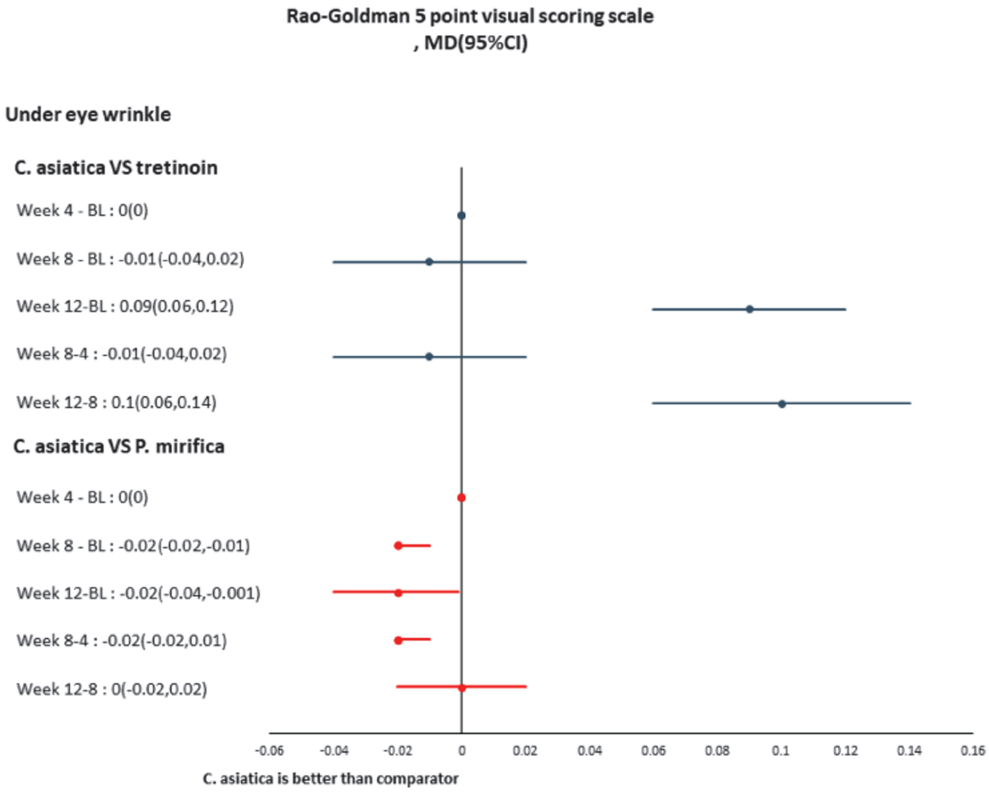

Figure 3. Under-eye wrinkles measured by the RG5VSS.

PARTICIPANT OPINION/SATISFACTION

All studies sought participant opinions about the treatment, but no meaningful detail about these was reported.

ADVERSE EVENTS

One study performed a pretrial 48-h skin patch test which produced no skin reactions (20) but reported AEs (erythema, burning, pain, or dryness) during the trial. *C. asiatica* treatment yielded 10 AEs compared with 35 cases with tretinoin, 18 at 4 w, 12 at 8 w, and five at 12 w (Table III). However, another study using a similar protocol and identical *C. asiatica* formulation reported no AEs. None of the AE reports had severity ratings. Other studies either did not mention AEs or specifically stated that no AEs were found. Trials suffered some dropouts: Lee et al. (18) lost two participants, and Tangsumroeng-wong (20) had three dropouts, but reason(s) for leaving were not reported. The dropout in Zhang et al. (22) had other commitments.

ADHERENCE TO TREATMENT.

No study reported on adherence to treatment.

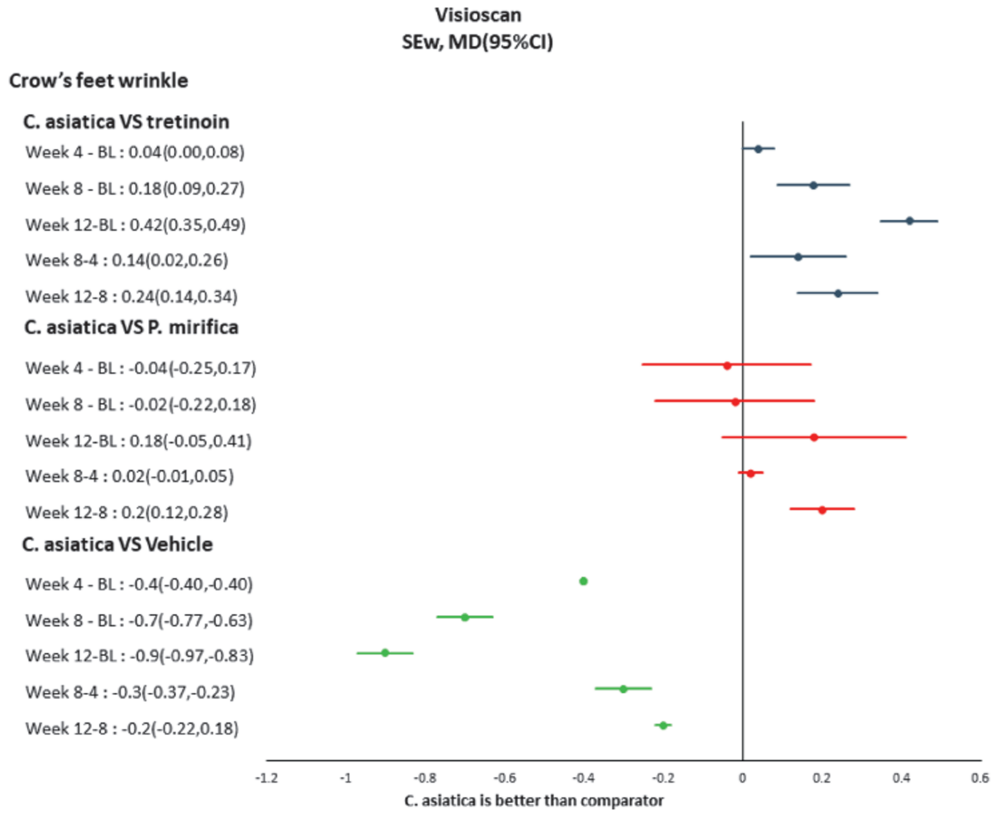

Figure 4. Lateral angle (crow's feet) wrinkles measured by Visioscan.

DISCUSSION

This is the first S.R. and N.M.R. study on cosmetics that investigated the effect of *C. asiatica* or its components as the sole active ingredient on wrinkles. The study suggests that *C. asiatica* or its pentacyclic triterpenoids reduce periorbital wrinkling. Furthermore, *C. asiatica* may be more effective than P. M. but possibly less than tretinoin. *C. asiatica* increased skin hydration, which might account for the anti-wrinkle action, whereas tretinoin had no such action.

Were the actions clinically useful? For cosmetics, the change in appearance is the most important endpoint. When this was assessed at 4-w intervals by independent blinded experts (dermatologists), or machine reading, wrinkling was consistently reduced in three studies (18,19,22). However, the effect sizes were small, including those by dermatologist assessment in Tangsumroengwong (20) and Tongsrikeaw (21), although the Visioscan has a narrow dynamic range when measuring wrinkles. Ultimately, participants and users need to assess whether they would feel the improved cosmetic appearance is enough to justify the cost of the preparation and the time devoted to twice daily applications, perhaps indefinitely. Most of the studies provided too little detail about participant self-assessment for users to draw any conclusions about their perceived efficacy of the treatments. We surmise that all studies were conducted on Asians (Korean, Thais, and

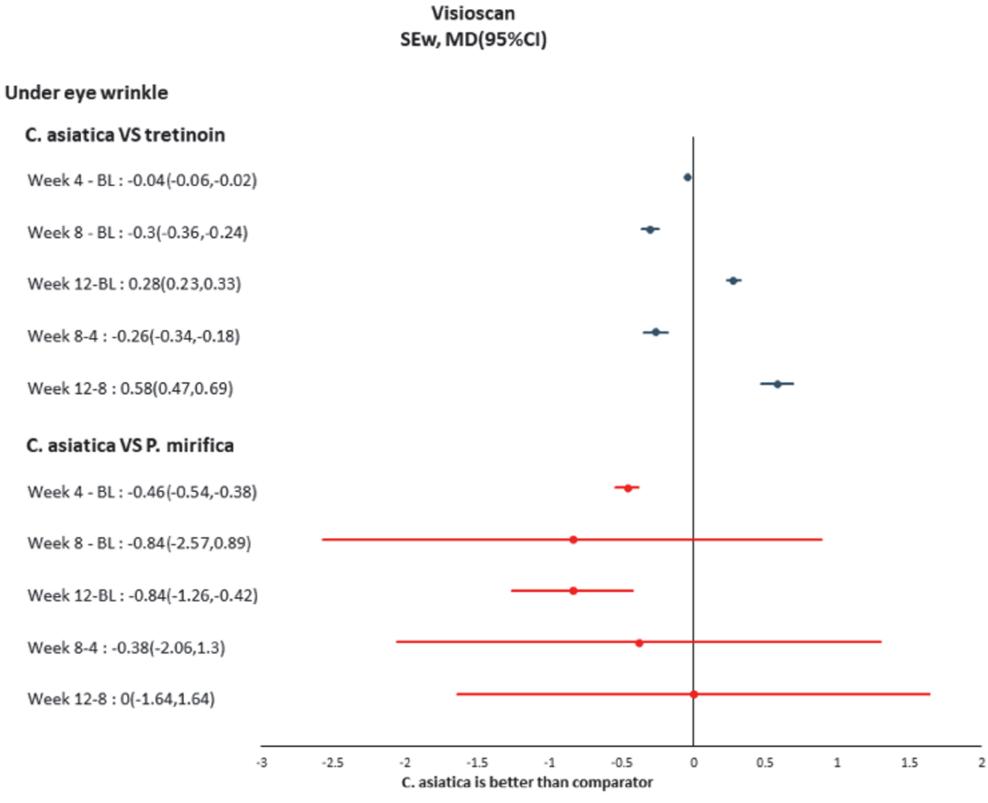

Figure 5. Under eye wrinkles measured by Visioscan.

Chinese). Even among Asians, wrinkling has some ethnic specificity (23); thus, the results have limited generalizability.

Detailed assessment of safety information derived from the studies was patchy. Thus, one study (20) found 10 AEs with *C. asiatica* extract, whereas another study (21) using the exact same preparation run in the same laboratory reported no AEs. Topical retinoids are well known for AEs; a greater safety for *C. asiatica* was suggested when tretinoin was the comparator (20), although information on AE duration and severity was not reported.

Although cellular actions of retinoids are understood, information is less clear for *C. asiatica* terpenoids. The triterpenes asiatic acid, asiaticoside, and madecassic acid are thought to mediate actions of *C. asiatica*. Asiatic acid has a bewildering list of molecular actions (24), and transforming growth factor β-receptor 1 kinase-independent Smad activation pathway involving collagen synthesis is a favored candidate for de-wrinkling skin (25).

Study quality using the Cochrane Risk of Bias tool suggested minimal bias. However, the depth of reporting was lamentable. All the studies fell well short of the CONsolidated Standards of Reporting Trials 2010 checklist. Inadequate reporting of methodologies made it difficult to assess protocol rigor, and in some cases, over-summarizing and pooling of data compromised interpretation. How adherence was encouraged and monitored was unclear, and thus would influence apparent effectiveness. Reporting of AEs was either nonexistent or inadequate. No study reported severity of AEs and extent, for example,

whether rashes were local or systemic. The *C. asiatica* versus tretinion trial (20) reported many AEs, but it is not clear whether multiple AEs coincided in the same participant at the same time and what constituted an AE (whether one AE continued through more than one 4-w period). Withdrawal criteria were unclear. Participant satisfaction questionnaires were not quantitated. Details about *C. asiatica* and P. M. extracts (plant source, processing methods, and how standardized), and, most importantly, the absence of ingredient reporting compromise study replication. These results are clinically non-translatable and not generalizable to *C. asiatica*. Nevertheless, other dermatological studies provide some clues about which active ingredients might be effective (12).

Our review also had some limitations. Of all studies discovered, only three were placebo-controlled RCTs testing a single ingredient. Two studies were found in Thai national archives, but databases and obscure repositories may exist elsewhere. The anti-wrinkle study cohorts were predominantly younger premenopausal women where the well-established role of estrogens contributes to cutaneous structure, function, immunity, and tissue repair. Thus, wrinkly, thin-skinned older women may respond differently exemplified by long-term use of tretinoin that remarkably improves skin structure (26). All the studies were short (8–12 w) and effects more noticeable at the longer times. Longer tretinoin exposures (>6 mo) show greater effect sizes (27) which may also apply to *C. asiatica*.

Future cosmetic studies should fully comply with CONsolidated Standards of Reporting Trials 2010 and its extension herbal medicinal interventions. Reporting must provide chromatographs quantitating the intervention contents, a complete participant flowchart, full clinical oversight, full compliance with the latest Declaration of Helsinki, adequate powering (minimum 20 per group), provide participants with a diary to note AEs, and verify adherence to the intervention, and placing the raw data in the public domain as required by many journals.

CONCLUSION

The topical application of *C. asiatica* extracts or of one of its components, asiaticoside, can improve several cosmetic outcomes, especially facial wrinkles. It may be an option for reducing periocular wrinkles and may avoid some AEs of tretinoin. Because the *C. asiatica* extract was not standardized, longer term studies are needed to rectify the deficiencies in the discovered studies and to establish acceptable long-term and generizable effectiveness and safety.

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