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REVIEW ARTICLE

A systematic review to evaluate the efficacy of azelaic acid in the management of acne, rosacea, melasma and skin aging

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Abstract

Background: Topical azelaic acid (AA) is indicated for acne and rosacea, but there is some evidence for its use for other dermatological conditions.

Aims: To assess the effectiveness and safety of topical AA for acne vulgaris, rosacea, hyperpigmentation/melasma, and skin aging.

Methods: RCTs of at least 6 weeks' treatment duration were eligible for inclusion. Databases including MEDLINE, Embase, CINAHL, and ClinicalTrials.gov were searched up to December 2022. Two reviewers were involved in all stages of the systematic review process.

Results: Forty-three RCTs met the inclusion criteria. Meta-analyses within 20 rosacea studies demonstrated that erythema severity, inflammatory lesion counts, overall improvement, and treatment success (achieving skin clarity) were significantly improved with AA compared with vehicle after 12 weeks. AA was more effective than metronidazole 0.75% for improved erythema severity, overall improvement, and inflammatory lesion counts. Sixteen acne studies suggest that AA is more effective than vehicle for improving global assessments and reducing acne severity. AA 20% also significantly reduced more lesions than erythromycin gel. Within seven melasma studies, AA 20% was significantly better than vehicle for both severity and global improvement. AA 20% demonstrated significantly better results compared with hydroquinone 2% for global improvement. Very few significant differences between AA and comparators were observed for commonly reported adverse events. No eligible RCTs were found that evaluated skin aging.

Conclusions: AA is more effective than vehicle for rosacea, acne and melasma. Comparisons between AA and other treatments were often equivalent. Where there is equivalence, AA may be a good option for some clinical situations. RCT evidence is needed to evaluate the effectiveness of AA on skin aging.

KEYWORDS
acne, azelaic acid, dermatology, melasma, rosacea

1 | INTRODUCTION

Azelaic acid (AA) is a dicarboxylic acid found naturally in barley, wheat and rye.[1] It is also produced by *Malasezzia furfur*, a skin commensal yeast that causes a skin condition called Pityriasis (Tinea) versicolor.[2] This yeast disturbs melanogenesis through inhibition of tyrosinase in the skin resulting in areas of hypopigmentation. AA also has anti-microbial and anti-comedonal properties[3] as well as a number of anti-inflammatory properties; it inhibits the production of reactive oxygen species and reduces proinflammatory cytokines including IL-1, IL-6 and TNF-a.[4]

Studies have also shown that AA can reverse UV-induced inflammatory reactions in the skin, which may explain why it is a useful agent in conditions, such as rosacea, which are triggered by sunlight in some people. In one study, AA significantly reduced the ultraviolet B light-induced nuclear translocation of nuclear factor kB p65 subunit and the phosphorylation of the p38 mitogen and stress-activated protein kinase. AA also induced peroxisome proliferators–activated receptor γ (PPARγ) activity, which has a crucial role in the control of inflammation.[5]

AA is currently widely licensed and recommended globally for rosacea and acne vulgaris (Table 1). It has also been used in melasma and post-inflammatory hyperpigmentation (PIH), especially with PIH associated with acne and in people with darker skin.[6] The objective of this systematic review was to create an up-to-date, high quality evidence base evaluating the effectiveness and safety of topical AA for acne, rosacea, melasma, hyperpigmentation, and skin aging. It is intended to inform good practice, as well as being a reference document for both patients and professionals.

2 | MATERIALS AND METHODS

This systematic review was undertaken according to the principles presented in the Cochrane handbook[16] and using guidance published by the Centre for Reviews and Dissemination (CRD).[17] The protocol was registered on PROSPERO (CRD42020220648).

Studies eligible for inclusion were randomized controlled trials (RCTs) of at least 6 weeks' treatment duration that compared topical AA (in any dose or form) with vehicle, another dose of AA (e.g.

TABLE 1 Azelaic acid in clinical guidelines.

Condition	Guideline	Recommendation
Acne	UK NICE guidelines[7]	First-line recommendation for azelaic acid in conjunction with oral antibiotics for moderate to severe acne. Second-line as a monotherapy for acne maintenance if adapalene/benzoyl peroxide combination is not tolerated
Acne	European S3 guidelines[8]	Azelaic acid recommended for: Comedonal acne (low strength) Mild -moderate papulopustular acne (moderate strength) Severe acne (recommended to be used) alongside oral antibiotics
Acne	Japanese guidelines[9]	Alternative (second-line) treatment for comedones and inflammatory acne lesions
Acne	American guidelines[10]	Recommended as an alternative to topical retinoids especially in Fitzpatrick skin types 4 or greater due to the benefit in post inflammatory hyperpigmentation or in pregnancy
Rosacea	UK BAD guidelines[11]	Recommend either ivermectin, metronidazole or azelaic acid as first-line topical treatment options to people with papulopustular rosacea.
Rosacea	Swiss guidelines[12]	Recommended for papulopustular rosacea and erythema
Rosacea	American guidelines[13]	Recommended in papulopustular rosacea as a monotherapy or with oral doxycycline in severe papulopustular rosacea
Melasma	UK Primary Care Society guidelines[14]	Azelaic acid 20% cream suggested as primary care treatment
Melasma	Chinese guidelines[15]	AA 15%–20% twice daily recommended for melanising-type melasma

AA 20% vs. AA 15%), or another medical treatment or procedure given to healthy adolescents or adults (12 years of age or older) (see Appendix S1 for a full list of selected comparators).

Outcomes of interest included improvement in facial rosacea, acne, melasma, hyperpigmentation, and measures of anti-aging (including improvements in photoaging, wrinkles, and dull skin). In addition, we included studies that evaluated AA in combination with other active medications versus those other medications alone. Any scoring system on treatment effectiveness was eligible.

In addition, adverse event data (including local skin reactions such as burning, pruritus, erythema, exfoliation, pain, dryness, discoloration, or irritation) and serious adverse event data (i.e. any reactions graded III or above by the study authors) were evaluated.

2.1 | Search strategy

To identify relevant trials, we searched MEDLINE, PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine (AMED), the TRIP database, the Cochrane Library (which includes the Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL)), NIHR Health Technology Assessment (NIHR HTA and other NIHR journals), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database from inception to December 2022.

In addition, we searched trials registries and gray literature (see Appendix S2 for details). The search was not restricted by country or language. Search terms included (but were not limited to) 'azelaic acid', 'Skinoren', 'Finacea', 'acne vulgaris', 'hyperpigmentation', 'melasma', 'anti-aging', 'photoaging', 'wrinkles', 'rosacea'. The full set of search terms (for MEDLINE) is presented in Appendix S2. The references of recent reviews were checked for additional trials not identified by the electronic search.

Two reviewers (SK and JC) independently screened the titles and abstracts identified in the literature searches. Full papers were obtained for these records and were assessed for relevance by two reviewers independently. The trials were critically appraised using the RoB 2 tool for RCTs[18] by two reviewers independently with any discrepancies resolved through discussion.

2.2 | Statistical analysis

Where appropriate, data were combined in a meta-analysis. To do this, means and standard deviations were collected for continuous outcomes and used to estimate study-specific and pooled mean differences with 95% confidence intervals (CIs). Numerators and denominators were collected for dichotomous outcomes, with Mantel–Haenszel (M-H) risk ratios (RRs) and 95% CIs used to summarize effect sizes.

Statistical heterogeneity was assessed using the χ^2 test and the I^2 statistic, and by examining the random effects between study variance (τ^2). We also conducted sensitivity analyses, excluding studies with a high risk of bias to assess the robustness of results. Where possible, the GRADE system[19] was used to provide an assessment of the quality of the body of evidence for each outcome.

2.3 | Results

In total, 43 RCTs met our eligibility criteria (see Figure 1 for details on the search and screening process and Appendix S3 for the list of excluded full-text studies with reasons for exclusion). Of these, 38 reported inter-individual comparisons and five were intra-individual RCTs, where each side of the face was randomized to a different treatment.

Twenty RCTs reported on outcomes for rosacea, sixteen reported outcomes on acne and seven reported outcomes on melasma. No RCTs were identified in the literature that specifically evaluated hyperpigmentation or anti-aging measures.

Twenty of the trials assessed AA 20% gel or cream, nineteen assessed AA 15% gel or foam, one evaluated AA 5% gel, and two trials did not report the dose of AA. Studies were conducted in the USA (35%), Iran (12%), and the UK (7%) as well as Canada, Italy, Germany, Turkey, Egypt, Pakistan, India, and the Philippines, or were multinational. Twenty-nine studies were conducted in adults, eleven were conducted in both adolescents and adults, and three did not report the age of the study participants. Six studies reported details on Fitzpatrick skin type.[20–25]

2.4 | Assessment of risk of bias

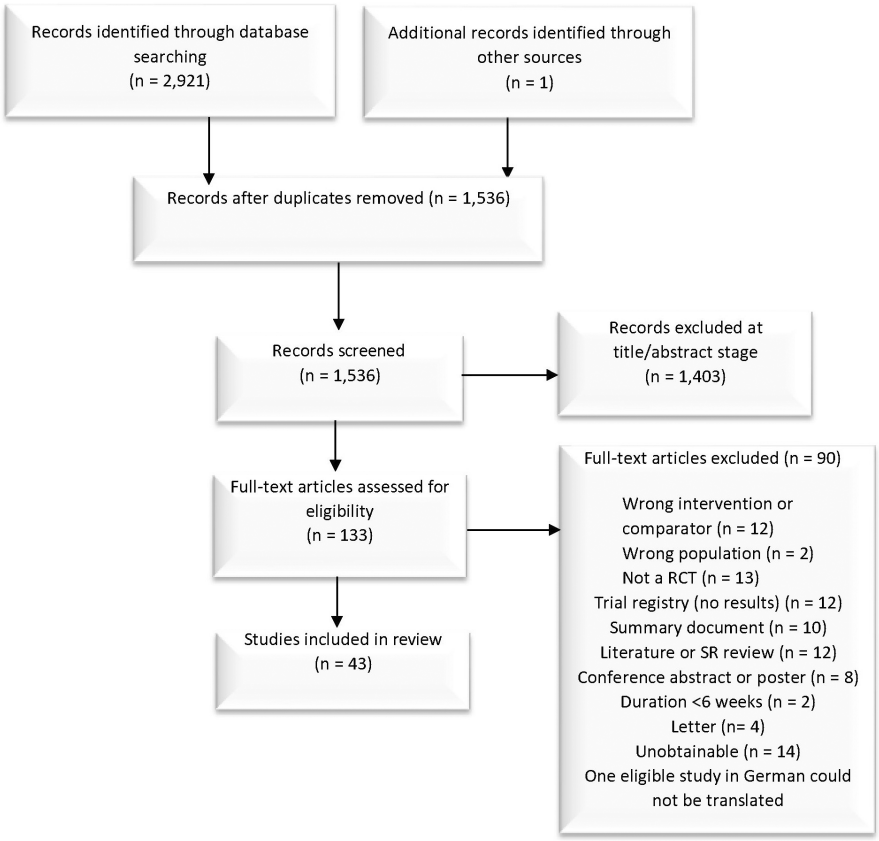
Using the RoB 2 tool and its associated Excel file with an algorithm, 37 RCTs were considered to have 'some concerns' in at least one area (e.g. due to the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, or selection of the reported result), and six were considered to have a high risk of bias due to different reasons including lack of allocation concealment, uneven and/or large participant withdrawals with per protocol analysis, or lack of blinding[22,23,26–29]; no studies were considered to have a low risk of bias (Figure 2).

3 | RESULTS

3.1 | Rosacea studies

Twenty RCTs with five different treatment comparisons were available for rosacea: AA vs. vehicle, metronidazole, permethrin, or brimonidine, AA plus Nd:Yag laser vs. Nd:Yag laser. They also compared treatment frequency; AA twice versus once daily. In terms of baseline characteristics, rosacea study participants were adults aged 18–83 (average age 49.7 years, where specified), 75.4% female, majority white (89.2%), and with moderate to severe rosacea.

FIGURE 1 Prisma flow diagram.



Rosacea study outcomes were assessed by improved erythema severity, lesion counts, overall improvement and treatment success.

3.1.1 | Improved erythema severity

There is consistent evidence that AA is more effective than vehicle for improving erythema (redness of the skin) severity. Of five studies that evaluated this comparison, three could be combined in a meta-analysis[30,31]; (Study 1 and Study 2). This analysis demonstrated that patients treated with AA 15% had improved erythema severity compared to those who received vehicle after 12 weeks. Pooled results: mean percentage of improvement of 51% in those using AA and 36% in the control groups (risk ratio [RR] 1.38 [95% CI: 1.12–1.71], $p=0.003$, 3 RCTs, $n=1624$; GRADE: moderate quality) (Figure 3). There was, however, statistical heterogeneity between the studies ($\tau^2=0.02$; $p=0.07$; $I^2=62\%$).

Two additional RCTs presented erythema severity using different analyses than those above,[28,32] but also found significant effects in favor of AA 20%, thus supporting the findings of the meta-analysis of AA 15%; AA 20% produced mean erythema severity score reductions of 48% versus 38% for vehicle in one study[28] and reductions of 8% for AA versus 5% for vehicle in the other.[32]

Based on the GRADE system, this entire body of evidence was low quality. None of these studies were considered to have a high risk of bias, so sensitivity analysis was not conducted.

No differences were observed for measures of erythema severity between once daily vs. twice daily AA 15% after 12 weeks (no data reported)[33] (GRADE: some concerns), AA 20% versus permethrin after 15 weeks (mean score of 1.1 with AA vs. 1.3 with permethrin, where 0 = none and 3 = severe)[22] (GRADE: low quality), and AA 15% versus brimonidine after 12 weeks (mean erythema severity score of 1.3 with AA versus 1.2 with brimonidine, where 0 = no erythema and 4 = very severe)[34] (GRADE: moderate quality).

The evidence was inconsistent across three trials that compared AA 20% (mean erythema score in one study of 1.1 with AA vs. 1.3 with metronidazole, where 0 = none and 3 = severe,[22] and mean score in a second study of 2.38 with AA versus 2.61 with metronidazole, where 1 = none and 4 = severe[35]) or AA 15% (improvement in erythema severity in 56% of AA group vs. 42% of metronidazole group)[36] versus metronidazole 0.75% after 15 weeks (GRADE: low quality).

3.1.2 | Inflammatory lesion counts

There is consistent, moderate quality evidence that AA (15% or 20%) is more effective than vehicle in reducing inflammatory lesion counts (i.e. papules and pustules) in patients with rosacea. Of ten studies, six studies could be included in a meta-analysis because their intervention and control group baseline counts were similar[28,30,37,38,31]; (Study 1 and Study 2). After 12 weeks of treatment, AA (15% and 20%) was found to significantly reduce lesions compared to vehicle,

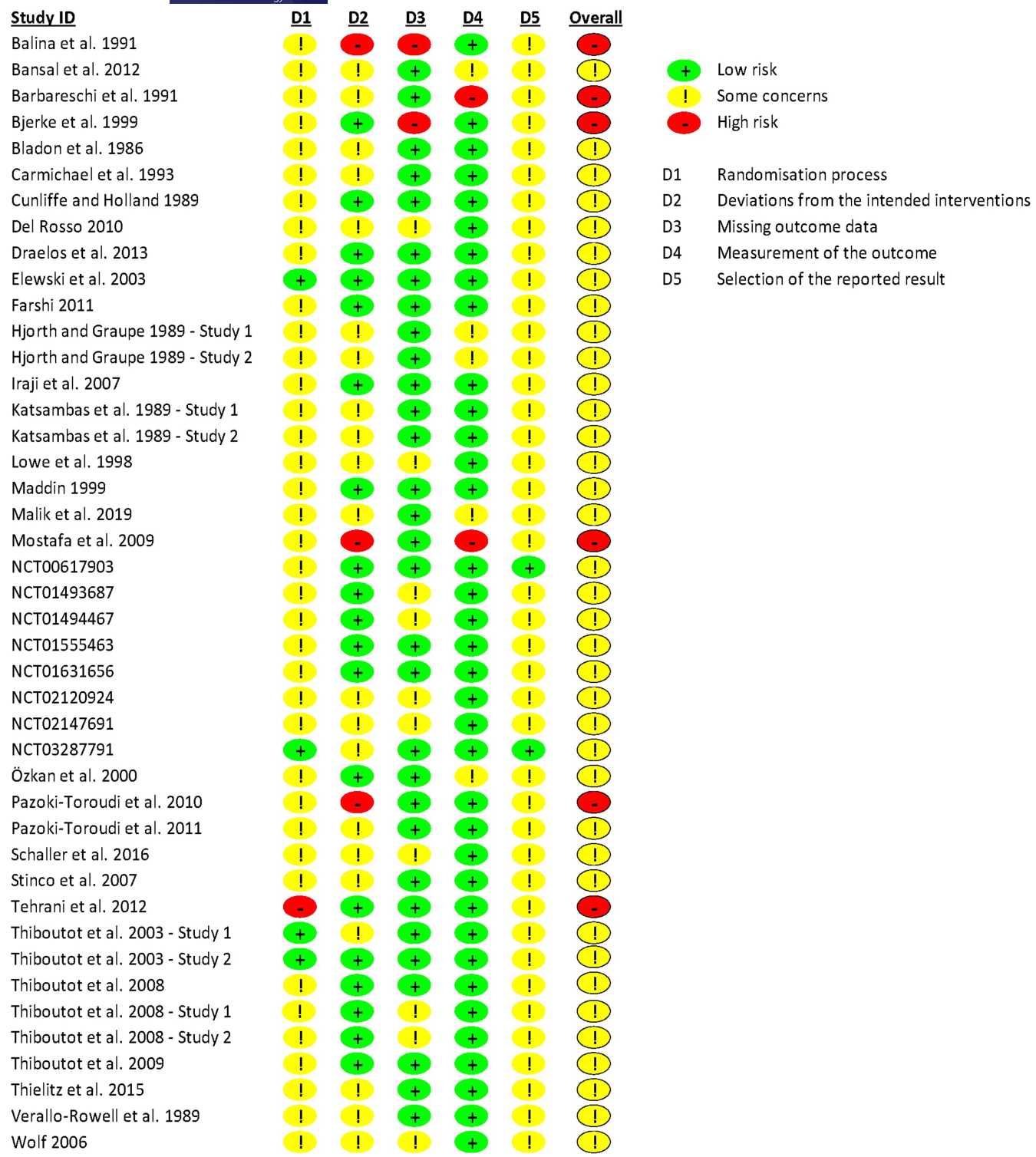


FIGURE 2 Risk of bias of the included Randomized Controlled Trials (RCTs).

with a pooled mean difference of −2.82 (95% CI: −3.64 to −2.00), $p < 0.0001$, 6 RCTs, $n = 2223$, GRADE: moderate quality. This equates to a mean reduction of 63% in the AA group and 48% with vehicle; the AA group had a mean inflammatory lesion count of 7.83 and vehicle 11.07, down from 21.23 and 21.17 at baseline. (Figure 4) No significant statistical heterogeneity was observed between these trials ($\tau^2 = 0.01$; $p = 0.41$; $I^2 = 1\%$). Sensitivity analysis, excluding one trial with a high risk of bias from the meta-analysis,[28] did not change the overall effect size. Nine to 12-week data from three other RCTs support the findings of the meta-analysis.[32,39,40]

One intra-individual study reported significantly reduced mean numbers of inflammatory lesions with AA 20% compared with permethrin 5% after 15 weeks and 6 months[22] (GRADE: moderate quality). Significant differences were not demonstrated for AA 15% vs.

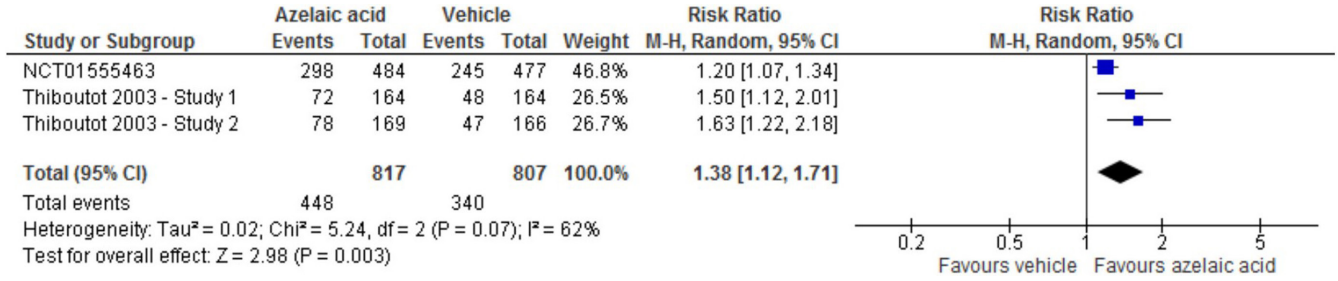


FIGURE 3 Proportion of rosacea participants with improved erythema severity: azelaic acid 15% versus vehicle.

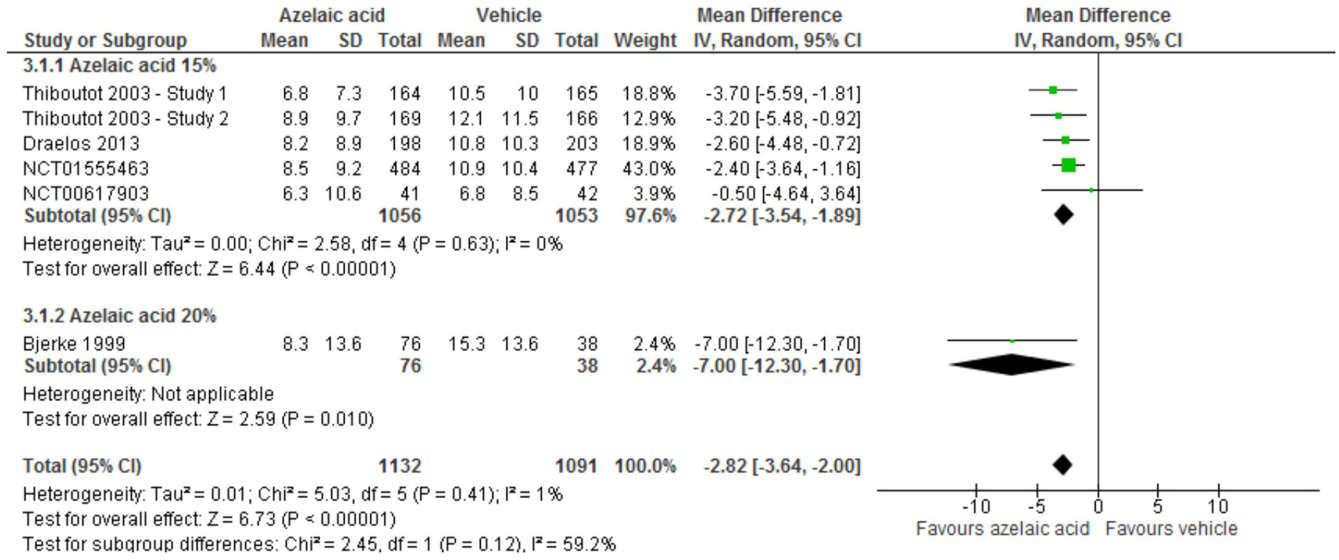


FIGURE 4 Mean inflammatory lesions at end of treatment for rosacea: azelaic acid (15% or 20%) versus vehicle. Some studies did not present standard deviations (SDs); in Bjerke et al. (1999), SDs were obtained from a p value. For Thiboutot et al. (2003) studies 1 and 2, and also NCT0155463, SDs were imputed using data from Draelos et al. (2013)

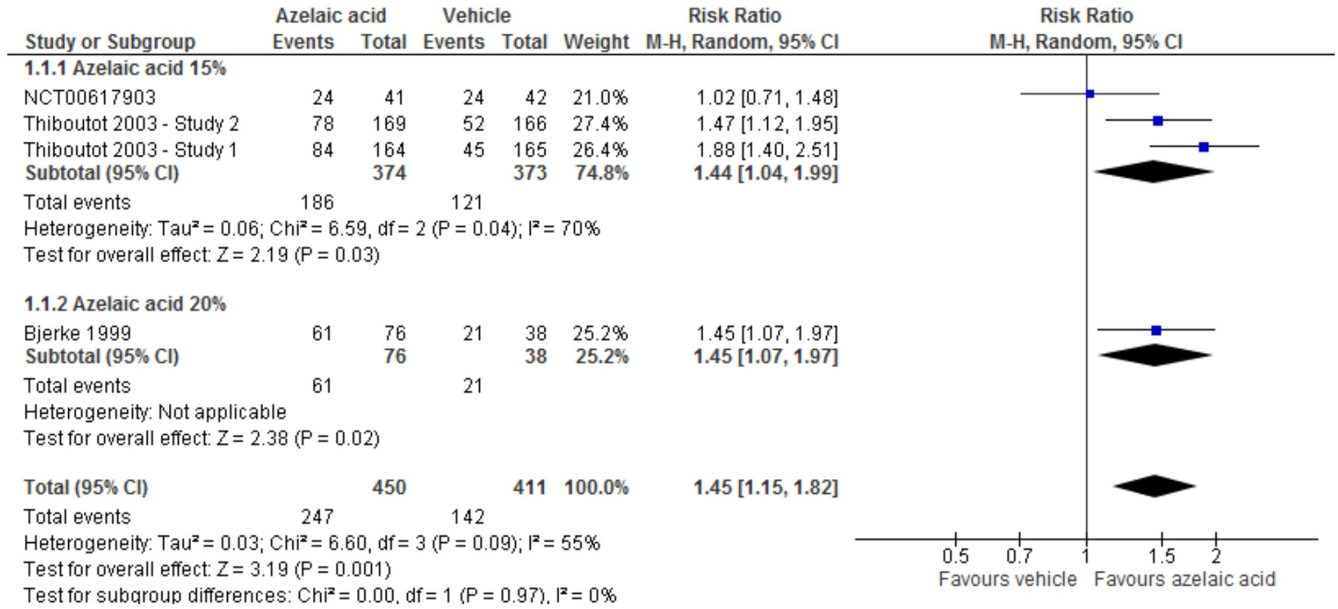


FIGURE 5 Overall improvement for rosacea as rated by a physician/investigator: azelaic acid (15% or 20%) versus vehicle.

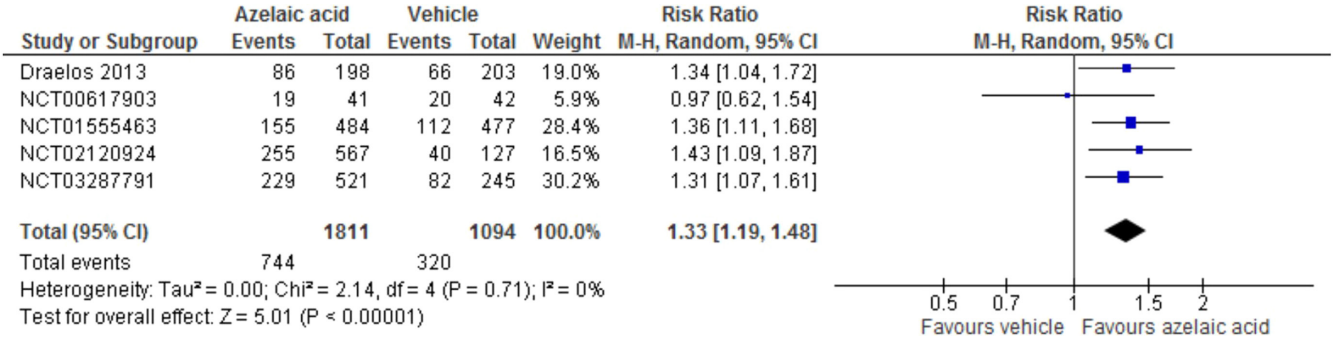


FIGURE 6 Treatment success for rosacea: azelaic acid 15% versus vehicle.

brimonidine gel 0.33% after 12 weeks.[34] There was consistent moderate quality evidence from three RCTs that AA 15% or 20% was more effective than metronidazole 0.75% at reducing mean lesion counts at 15 weeks, although mean differences were small.[22,35,36] One RCT reported no difference in lesion counts between those who received AA 15% and metronidazole 1% after 12 weeks[41] (GRADE: some concerns).

3.1.3 | Overall improvement

This measure includes erythema severity as well as other outcomes, such as the number of small and/or large papules and pustules. Overall improvement in rosacea as assessed by a physician was better with AA (15% or 20%) compared with vehicle, although the evidence is of low quality. Two trials reported on the proportion of patients who had 'complete remission or a marked improvement'[28,37] and the other two reported on the percentages who had 'good to excellent' ratings[31] (Study 1 and Study 2). The pooled results from these four trials demonstrated a RR of 1.45 (95% CI: 1.15–1.82), ($p=0.001$, $n=861$), in favor of AA (15% or 20%) compared with vehicle after 12 weeks of treatment (Figure 5); that is, those using azelaic acid were 1.5 times as likely to experience complete remission, a marked improvement, or 'good to excellent' ratings than those receiving vehicle.

There was statistical heterogeneity ($\tau^2=0.03$; $p=0.09$; $I^2=55\%$). One study in this analysis was considered to have a high risk of bias,[28] which when removed from the analysis did not change the overall effect size. Results from one intra-individual RCT[32] were also consistent with the meta-analysis.

Improvement was not reduced or altered depending on treatment frequency or between AA 15% twice daily vs. AA once daily after 12 weeks (no data reported)[33] (GRADE: moderate quality). AA 15% versus brimonidine after 12 weeks (mean Investigator Global Assessment (IGA) score 1.3 for AA and 1.4 for brimonidine – 0 is 'clear' and '4' is 'severe')[34] (GRADE: moderate quality), and AA 15% plus Nd:Yag laser vs. Nd:Yag laser only after 6 weeks (mean IGA score 3.1 for AA+laser and 3.5 for laser only—0 is 'clear' and 6 is 'severe inflammatory signs of rosacea')[42] (GRADE: moderate quality).

Two trials reported significantly better global improvement with AA (15% or 20%) compared with metronidazole 0.75% after 15 weeks (in the first trial, scores of ~2.8 for AA vs. ~3.2 for metronidazole (scores based on data captured from a figure), where 0 is '100% clearance of disease signs and symptoms' and 6 is 'exacerbation'[35] and in the second trial, 'excellent or complete remission' in 48% with AA vs. 35% with metronidazole)[36] (GRADE: moderate quality). Two trials that compared AA 15% with of metronidazole did not observe significant differences between the treatment groups (in the first trial, 19% of AA patients 'completely cleared' vs. 21% with metronidazole[25] and in the second trial, 'excellent improvement' in 47% with AA vs. 42% with metronidazole – both groups were also receiving doxycycline 40 mg in this trial[41]) (GRADE: moderate quality).

3.1.4 | Treatment success: achieving 'skin clear or nearly clear' results

Treatment success was considered as the number of patients who had clear or minimal scores according to the Investigator's Global Assessment (IGA) scale at the end of treatment. Seven rosacea trials assessed treatment success after 12 weeks.

There is high quality evidence that AA 15% is more effective than vehicle based on a meta-analysis of five RCTs (RR was 1.33 (95% CI: 1.19–1.48), $p<0.00001$, $n=2905$, with no statistical heterogeneity observed between the trials ($\tau^2=0.00$; $p=0.71$; $I^2=0\%$))[30,37–40] (Figure 6). None of these studies were considered to have a high risk of bias, so sensitivity analysis was not conducted.

3.1.5 | Use of azelaic acid as maintenance therapy in rosacea

One multicentre study assessed the efficacy of azelaic acid 15% as a maintenance therapy in rosacea.[43] In the initial open-label, non-randomized phase of the study, subjects ($n=172$) received topical AA 15% gel and oral doxycycline (100 mg), both twice daily, for ≤12 weeks. After 4 weeks of combination treatment, physicians rated overall improvement as good, excellent or complete remission in 42% of participants. At the end of 12 weeks, 13% of participants

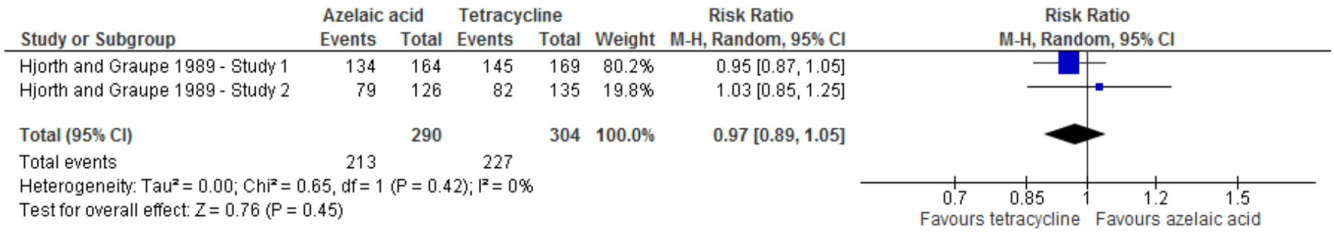


FIGURE 7 Global improvement for acne: azelaic acid 20% versus oral tetracycline.

were judged to be in complete remission; a further 44% had excellent improvement, 18% had good improvement and 21% experienced moderate improvement.

In the second, double-blind study phase, subjects who had initially undergone at least 4 weeks of combination treatment in phase 1 and who reduced their inflammatory lesion count by ≥75% ($n=136$) were randomized to receive either AA 15% gel or its vehicle twice daily for 24 weeks. The deterioration in inflammatory lesion count during maintenance treatment was less with AA 15% gel than with vehicle, with significant superiority in the AA group beginning in week 8 of phase 2 ($p=0.01$) and persisting through week 16 ($p=0.02$), 20 ($p=0.001$) and 24 ($p=0.03$). Erythema and telangiectasia scores remained unchanged from baseline to study end in both groups.

3.2 | Acne studies

Sixteen RCTs collectively assessed ten different treatment comparisons for acne vulgaris: AA vs. vehicle, tretinoin, erythromycin, adapalene, benzoyl peroxide, benzoyl peroxide and clindamycin, tetracycline, or clindamycin, or AA for 9 months versus 3 months, or low dose AA plus clindamycin vs. clindamycin alone. The included participants were aged 11–50 years with a mean age of 21 years where specified, 53% were female, and the participants had mild to moderate acne; breakdown by ethnicity was only reported in one study.

Three main outcomes were reported: reduction in lesion count, global improvement and reduction in severity. Given methodological differences between these studies, only one meta-analysis could be conducted.

3.2.1 | Reduction in lesion counts

Data on lesion counts, either as absolute counts or percentage reductions from baseline, were presented for ten different treatment comparisons in the studies on acne. There is evidence from five RCTs to suggest that AA 20% is more effective than vehicle at reducing lesions; the mean percentage reduction in comedones in 4 of the 5 studies was 70% with AA and 14% with vehicle (Katsambas 1989 only expressed median percentage change and no information on lesion counts was provided)[26,29,44–46] (low to moderate quality evidence).

Significant differences were observed in favor of low dose of AA 5% plus clindamycin when compared with clindamycin alone after 12 weeks (63% mean reduction in lesion count with AA-clin compared with 47% with clindamycin alone)[47] (GRADE: high quality).

AA 20% demonstrated significantly better results compared with erythromycin gel 2% after 12 weeks (a 53% reduction in papules with AA vs. 39% with erythromycin, 53% vs. 41% reduction in pustules, and 89% vs. 80% reduction in comedones)[29] (high risk of bias), and combined benzoyl peroxide 3% and clindamycin 1% gel demonstrated better results compared with AA 20% after 12 weeks (52% reduction in total inflammatory lesion count with BPO/clindamycin vs. 38% with AA)[48] (GRADE: high quality).

Reductions in total lesions, inflammatory and non-inflammatory lesions were better for 9 months versus 3 months treatment of AA 20%, but no statistical results could be calculated[49] (GRADE: some concerns). No significant differences were observed between AA 20% versus tretinoin 0.05% at 6 months[46] – Study 2 (GRADE: some concerns), AA 15% versus benzoyl peroxide 5% at 2 or 4 months[50,51];– Study 1 (GRADE: moderate quality), AA 20% versus oral tetracycline at 5 or 6 months[52] – Study 1 and 2 (GRADE: high quality), or AA 15% versus clindamycin 1%[51]– Study 2 (GRADE: some concerns). Results were inconsistent for comparisons between AA versus adapalene 15% (one study did not report a dose) at 2 months or at 36 weeks[49,50] (GRADE: moderate quality).

3.2.2 | Global improvement

Various assessments of global (overall) improvement for acne were observed across six different treatment comparisons. These were largely reported as the proportion of patients with 'good or excellent' response, or similar. Significant improvements were observed with AA 20% versus vehicle at 3 months (64% of AA patients had 'good to excellent improvement' versus 36% with vehicle)[46] – Study 1 (GRADE: high quality), with combined benzoyl peroxide 3% and clindamycin 1% versus AA 20% at 12 weeks (82% improved and 58% 'much improved' or 'very much improved' with AA versus 73% improved and 43% 'much improved' or 'very much improved' with BPO/clindamycin)[48] (GRADE: high quality), and also with benzoyl peroxide 5% versus with AA 15% (64% had 'good' or 'very good' results with AA vs. 78% with BPO; time point of assessment not reported)[51] – Study 1 (GRADE: high quality).

Two RCTs compared AA 20% vs. oral tetracycline; one was conducted in patients with moderate acne[52] (Study 1), and the other in patients with moderate to severe acne[52] (Study 2). Pooled data demonstrated no significant difference between AA 20% and oral tetracycline

in the proportion of patients who achieved 'good or excellent improvement' at five or six months: RR 0.97 (95% CI: 0.89–1.05), $n=594$ (GRADE: high quality) (Figure 7). No significant statistical heterogeneity was observed between these trials ($T^2=0.01$; $p=0.65$; $I^2=0\%$).

3.2.3 | Reduction in severity

Data on acne severity were available for five different treatment comparisons: AA 20% was found to be significantly more effective than vehicle after 6 weeks (AA was 3.06 times more effective than vehicle in terms of Acne Severity Index (ASI) scores)[45] (GRADE: some concerns).

Low dose AA (5%) plus clindamycin gel 2% was significantly more effective than clindamycin alone after 12 weeks (64% reduction in Acne Severity Index (ASI) with AA + clindamycin vs. 48% with clindamycin alone)[47] (GRADE: moderate quality), and benzoyl peroxide 3% plus clindamycin 1% gel was significantly more effective than AA 20% after 12 weeks (percentage of patients 'clear' or 'almost clear' on Investigator Global Change Assessment was 17.6% for AA vs. 33.6% for BPO/clindamycin)[48] (GRADE: high quality). In addition, one trial reported a significant improvement in favor of topical clindamycin phosphate compared with AA after 8 weeks (doses not reported)[53] (GRADE: some concerns), and another found that oral tetracycline was more effective than AA 20% in reducing mean acne grades after 6 months, but a statistical comparison was not reported, and could not be calculated[54] (GRADE: some concerns).

3.3 | Melasma studies

Seven RCTs were included that collectively assessed four different treatment comparisons for melasma: AA versus vehicle, hydroquinone, or tranexamic acid, and AA versus low-fluence Q-switched Nd: YAG laser versus AA plus laser. Study participants had a mean age of 35 years where specified, 95% were female, the participants had Fitzpatrick skin types II–V, and were mostly Asian/Middle Eastern, Hispanic or Black.

Three commonly reported outcomes were assessed: melasma severity, global improvement and lesion size reduction. No meta-analyses could be undertaken.

3.3.1 | Melasma severity

One trial that compared AA 20% vs. vehicle reported on melasma severity at 24 weeks, but the results differed depending on the method used to assess severity; mean differences from baseline did not differ between groups when measured using an investigator's subjective scale, but did statistically differ when measured using a chromometer (to measure pigment intensity) in favor of AA, although the difference was small (AA 4.3 at baseline and 3.4 at 24 weeks vs. vehicle 5.4 at both baseline and 24 weeks)[21] (GRADE: some concerns).

Reduction in pigmentation intensity when measured by reductions in levels (i.e. by 2 or 3 levels using a 5 point scale) did not significantly differ between AA 20% versus hydroquinone 2% at 24 weeks[24] (GRADE: high quality), or between AA 20% versus hydroquinone 4% at 24 weeks.[27]

Another study that compared AA 20% and hydroquinone 4% reported significantly reduced pigmentation with AA after 2 months when assessed using the Melasma Area and Severity Index (MASI), with a 50% reduction in MASI score with AA versus 14% with hydroquinone[55] (together, the studies of hydroquinone 4% were considered to be of very low quality).

A further RCT compared AA 20% plus hydroquinone 5% versus hydroquinone 5% and reported a significant difference in mean MASI score reductions after 4 months in favor of combined treatment (69% reduction with combined treatment vs. 58% for hydroquinone alone)[23] (GRADE: some concerns).

In one study, two groups were either treated with oral tranexamic acid (250 mg twice daily) with topical 3% tranexamic acid (twice daily) or oral tranexamic acid (250 mg twice daily) with topical 20% azelaic acid (daily) for 6 months. They were followed every second month up to 6 months and the efficacy was assessed on the basis of MASI scores. Topical tranexamic acid 3% was more effective than AA 20% at 6 months, but not at 2 or 4 months[56] (GRADE: high quality).

No significant differences were observed between AA 20% and low-fluence Q-switched Nd: YAG laser at 6 or 12 weeks, however, those who received both laser and AA had significantly better MASI scores at 6 and 12 weeks compared with laser alone ($p=0.004$ and $p=0.000$, respectively)[20] (GRADE: some concerns). Combined treatment was also significantly better than AA alone at 12 weeks.[20]

3.3.2 | Global improvement

AA 20% was found to be more effective than vehicle at weeks 12, 20 and 24 for measures of global (overall) improvement (using a score from 0 to 8, e.g. 2.0 for AA at week 24 vs. 3.8 for vehicle)[21] (GRADE: some concerns). AA 20% was also found to be more effective than hydroquinone 2% at 24 weeks in the proportion of patients who achieved 'excellent/good' results (73.8% AA vs. 19.4%)[24] (GRADE: high quality), but not when compared with hydroquinone 4% (64.8% AA vs. 72.5%)[27] (GRADE: moderate quality). The proportion who achieved 'excellent/good' results was also not significantly different between AA 20% plus 250 mg oral tranexamic acid vs. topical tranexamic acid 3% plus 250 mg oral tranexamic acid (timepoint of assessment was not reported)[56] (GRADE: high quality).

3.3.3 | Lesion size reduction

Only two RCTs presented data on lesion size reduction: one compared AA 20% cream with hydroquinone 4%[27] (GRADE: moderate

quality), and the other that compared AA 20% with hydroquinone 2%[24] (GRADE: moderate quality). Both reported results at 24 weeks and found that the proportion of patients who had a reduced lesion size by >50% did not significantly differ between groups.

3.4 | Skin aging studies

No studies on azelaic acid and skin aging met the inclusion criteria. While there are a handful of published studies investigating the use of azelaic acid in conjunction with other ingredients, for example, a 2022 study wherein three active compounds resulted in a significant improvement in erythema and hyperpigmentation,[57] none are RCTs and no studies have been conducted on the use of azelaic acid as a monotherapy in skin aging.

3.5 | Adverse events

3.5.1 | Serious adverse events

Eighteen out of 20 RCTs in rosacea patients presented data on serious adverse events (SAEs) (i.e. grade III or above). Of these 18, 13 reported that none were experienced with AA. Across the remaining five trials, SAEs ranged from 0.26% to 3.8% in people applying AA 15%. Most were unlikely to be treatment related.[25,39,40,58,59] None of the studies concerning melasma presented data on SAEs, and only one study in acne patients reported that 2.8% of patients treated with AA 20% experienced an SAE,[60] but it is not clear if this was related to the treatment.

3.5.2 | Adverse events

Where possible, we calculated effect sizes between AA and comparators, but very few significant differences were observed for commonly reported adverse events. In summary, those treated with AA 15% experienced significantly worse itching and pain compared with vehicle, worse itching, dryness and irritation compared with ivermectin, and higher total adverse events (i.e. all adverse events combined) compared with metronidazole 0.75%. Those treated with AA 20% experienced significantly worse burning compared with hydroquinone 4%, and worse itching and pain compared with combined benzoyl peroxide 3% and clindamycin 1% gel.

4 | DISCUSSION

4.1 | Main findings

This systematic review has demonstrated that AA is significantly more effective than vehicle for improving erythema severity and reducing inflammatory lesion counts in patients with rosacea; global (overall) improvement and treatment success (skin clear or nearly clear) are also significantly higher in AA than with vehicle. Azelaic acid may also be a useful adjunct to oral antibiotics in rosacea and there is evidence for its use as a maintenance therapy.[43]

In acne, there is evidence to suggest AA's superiority over vehicle in terms of reducing lesion counts and in global improvement and reduction in severity. Results were inconsistent for adapalene versus AA, while there was no significant difference in efficacy between AA and tretinoin, AA and benzoyl peroxide, AA and topical clindamycin, or AA and oral tetracycline. AA demonstrated superiority over topical erythromycin based on evidence from one study.

AA reduces melasma severity and is more effective than vehicle and hydroquinone 2% in terms of global improvement. When combined with hydroquinone, AA reduces melasma severity compared to hydroquinone used alone. AA demonstrated significantly better global improvement compared to metronidazole in two studies, but there were no significant differences between the two treatments in a further two studies.

No evidence was published evaluating the efficacy of AA in anti-aging, and this is an area for future research.

This systematic review has shown azelaic acid to be an effective treatment with no or low serious side-effects. From a clinician's perspective, it may be important to consider a few clinically challenging situations where AA may be good option:

a. in pregnancy where topical retinoids are contraindicated,
b. to control acne and limit post-inflammatory hyperpigmentation (PIH), especially in skin of color (given the action of AA on the production of melanin in melanosomes),
c. in patients with sensitive skin or atopic dermatitis who cannot tolerate topical retinoids or benzoyl peroxide.
d. in patients with mild localized papulopustular rosacea (PPR) or in rosacea where the predominant symptom is erythema. This is because treatments with brimonidine gel are often not tolerated and can cause such profound vasoconstriction that dilated telangiectatic vessels (which are not sensitive to the gel) are simply rendered more visible, as the background erythema is ablated. Beta blockers by mouth are not ideal and often cause side-effects or are contraindicated, and physical treatments (such as pulsed dye laser or intense pulsed light) are not available on the NHS in the UK.

There is another important point to consider when prescribing for these conditions. There are increasing concerns about antimicrobial resistance, driven by the overuse of antibiotics both topically and systemically, especially for inflammatory skin conditions such as acne and rosacea. The evidence presented in this paper should encourage clinicians to consider AA before prescribing an antibiotic.

4.2 | Strengths

The strength of this up-to-date review is that a rigorous methodology was used to identify, screen, data extract and summarize the

studies, with a combination of meta-analysis and narrative synthesis used to analyze the evidence. Azelaic acid was considered as a treatment modality for acne, rosacea, melasma and skin aging, making this systematic review unique in its approach of examining the evidence for azelaic acid as a treatment for several different common skin conditions.

4.3 | Weaknesses

There may be some risk of publication and language biases. As per our protocol, we reported here the most frequently used outcomes, so some data reported in the literature may have been missed. We argue, however, that the main outcomes of importance have been captured, and have included outcomes not reported in other systematic reviews.

Very few studies have been conducted in the last 10 years, and the quality of the evidence is variable. For several outcomes, data are only available from a single trial. Studies conducted in pregnant or breastfeeding women were also lacking. When evaluating effectiveness, it is possible that results can differ depending on the timing or method used to assess an outcome.

4.4 | Comparison to other studies

4.4.1 | Rosacea

A previous systematic review also found that AA demonstrated a 'substantial benefit' in decreasing mean inflammatory lesion counts in patients with papulopustular rosacea with participants experiencing significant reductions in mean counts compared to vehicle ($p < 0.05$; our analysis a found similar result with a pooled mean different in lesion counts of −2.82, $p < 0.0001$). They also concluded that AA is 'an equally effective, if not better, treatment option' than metronidazole for PPR'[61] (our analysis found inconsistent evidence for AA vs. metronidazole). Another systematic review on rosacea also reported that physician-assessed improvement was significantly better with AA than with vehicle (57% deemed 'marked' or 'excellent' with AA vs. 40% with vehicle, RR = 1.40, cf. RR = 1.45 in our meta-analysis) and that there was 'little-to-no' difference in the proportion of patients with adverse events.[62]

4.4.2 | Acne

One recent systematic review by Liu et al. also presented data on the effectiveness of AA compared with placebo or no treatment and other active treatments for acne[63]. This study included the same studies we have reported on here, although we did not include conference papers. We note that our effect sizes may differ from those in Liu et al. because we employed a slightly different Cochrane methodology, and because of differences in how outcomes were categorized. However, their narrative summary is similar to ours, with both finding similar efficacy in AA and tretinoin (RR = 0.94 in Liu et al.).

4.4.3 | Melasma

A systematic review reported similarly to this review that there was no significant difference in improvement for melasma when AA 20% was compared to hydroquinone 4%, but that AA 20% was more effective than 2% hydroquinone (RR = 1.25).[64]

4.5 | Conclusions

This systematic review demonstrates that AA is more effective than vehicle for rosacea, acne and melasma. Comparisons between AA and most other active treatments were often equivalent, depending on the condition and outcome assessed. Where there is equivalence, AA may be a a good option for some clinical situations, for example in cases where patients are not able to tolerate equivalent treatments, or where another treatment is not considered to be safe for use in pregnancy. Although there were very few significant differences between AA and comparators for commonly reported adverse events, it is important for clinicians to know that there are potential side effects, including itching and pain. Further research is needed on the role of azelaic acid in anti-aging.

AUTHOR CONTRIBUTIONS

Rebecca Rowe conducted the searches for this review. Sarah King and Jo Campbell performed the study selection and data extraction processes, assessed the quality of included studies and conducted meta-analysis and narrative synthesis. Marie-Louise Daly, George Moncrieff and Catriona Maybury provided clinical and dermatological expertise and background. The manuscript was primarily written by Sarah King, Rebecca Rowe and Catriona Maybury.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

As this systematic review does not include any patient data, it was not necessary to obtain consent from human subjects or submit the study for ethical approval. As is good practice, the review protocol was registered on PROSPERO, and the review was conducted according to PRISMA standard.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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