



**OPTIMISING THE DELIVERY SYSTEM FOR EXOSOME THERAPY IN
SCAR MANAGEMENT: STANDARDISATION OF DELIVERY METHODS
AND OPTIMAL DOSING IN ACNE SCARRING : A SYSTEMATIC REVIEW
OF RANDOMISED CONTROLLED TRIALS AND PRIMARY STUDIES**

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ABSTRACT

Introduction: Atrophic acne scarring affects a substantial majority of patients with inflammatory acne and remains one of the most refractory indications in aesthetic and reconstructive dermatology. Mesenchymal stromal cell-derived and plant-derived exosomes are 30–150 nm extracellular vesicles that carry microRNA, growth-factor, and lipid cargo capable of suppressing transforming growth factor-beta 1 (TGF- β 1)/SMAD2-3 signalling, reprogramming macrophages towards an M2 phenotype, and restoring organised type I and type III collagen deposition. Their clinical translation, however, is constrained less by intrinsic bioactivity than by the physics of cutaneous delivery: the 15–20 μ m stratum corneum is an efficient exclusion filter for nanoscale vesicles. No previous synthesis has interrogated the delivery system itself as the principal determinant of clinical effect, nor

mapped the completeness of dose reporting across the human evidence base.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs included randomised controlled trials, cohort studies, case-control studies, cross-sectional studies, and other observational designs reporting exosome or exosome-like extracellular-vesicle therapy delivered to human skin for scar, post-acne, or dermal-remodelling indications. Two reviewers independently screened, extracted, and appraised.

Results: Eighteen primary studies enrolling 472 participants met the eligibility criteria: ten randomised controlled trials (seven split-face, three parallel-group), five prospective observational studies, and three case series. Six randomised comparisons provided extractable data for the primary outcome. The pooled standardised mean difference for global clinical improvement with exosome-augmented delivery versus the identical platform without exosomes was 0.82 (95% CI 0.50–1.13; $Z = 5.00$; $p < 0.000001$; $I^2 = 62.1\%$). The ablative fractional CO₂ laser subgroup yielded a pooled estimate of 0.64 (95% CI 0.40–0.87) with complete homogeneity ($I^2 = 0\%$). Every comparison in which the delivery platform transiently breached the stratum corneum favoured the exosome arm, whereas the only randomised comparison of topical application to an intact barrier produced a limited and time-decaying effect. Only 16.7% of studies reported any quantitative dose metric, and no study reported dose per unit treated area.

Conclusion: Exosome therapy delivers a clinically meaningful and statistically significant incremental improvement in scar and dermal-remodelling outcomes when—and, on present evidence, only when—it is administered through a delivery platform that

transiently breaches the stratum corneum. Device-assisted delivery should therefore be regarded as an obligate component of the intervention. An optimal dose cannot be defined from the existing literature; the field requires a mandatory minimum reporting dataset specifying particle concentration, total particle dose, protein content, treated surface area, characterisation against MISEV criteria, and potency assay results before dose-response modelling becomes possible.

Keywords: exosomes; extracellular vesicles; atrophic acne scar; drug delivery systems; microneedling; ablative fractional carbon dioxide laser; systematic review

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INTRODUCTION

Background

Acne vulgaris is among the most prevalent dermatological disorders worldwide, and permanent atrophic scarring is its most consequential sequela, affecting a majority of patients with a history of inflammatory disease. The psychosocial burden is disproportionate to the physical lesion: post-acne scarring is consistently associated with impaired self-esteem, social withdrawal, depressive symptomatology and reduced occupational confidence, and unlike active acne it does not remit spontaneously. Despite four decades of device development, no single modality reliably restores normal dermal architecture, and contemporary network meta-analysis of fifty-six randomised trials across thirty-four interventions confirms that combination strategies consistently outperform monotherapy while no single combination is definitively superior.^{21,26}

The pathophysiology of atrophic scarring explains this therapeutic ceiling. Scar formation follows a deficient rather than an exuberant reparative response: inflammatory destruction of the follicular unit and the surrounding dermis is followed by insufficient collagen deposition, disorganised extracellular-matrix assembly, persistent matrix-metalloproteinase activity and tethering of the scar floor to underlying fibrous septae. Interventions that act purely by mechanical disruption or thermal injury — subcision, ablative and non-ablative fractional lasers, microneedling, radiofrequency microneedling and chemical reconstruction — initiate a fresh wound-healing cascade but do not supply the biological signals that determine whether that cascade terminates in organised regeneration or in renewed fibrosis. This is the logical rationale for pairing an energy-based or mechanical delivery platform with a bioactive regenerative payload.^{20,21,26,39-43}

Exosomes are the smallest and most intensively studied subset of extracellular vesicles, measuring approximately 30–150 nm and originating from the endosomal multivesicular body. They carry a defined cargo of microRNA, messenger RNA, lipids and proteins, and constitute the principal paracrine effector arm of mesenchymal stromal cell therapy. In cutaneous repair, mesenchymal stromal cell-derived exosomes have been shown to suppress myofibroblast

transdifferentiation by delivering miR-21, miR-23a, miR-125b and miR-145, which inhibit the TGF- β 2/SMAD2 axis; to inhibit TGF- β receptor types I and II through miR-21-5p and miR-125b-5p; to promote angiogenesis and M2 macrophage polarisation; and to increase type I collagen while suppressing MMP-1 and MMP-3. Compared with the parent cell, exosomes offer lower immunogenicity, no tumorigenic or engraftment risk, superior storage stability and a dose that is in principle controllable.^{27,28,47-50,61,65}

Plant-derived exosome-like nanovesicles have emerged as a parallel and regulatorily distinct class. Preparations from *Rosa damascena*, *Panax ginseng*, *Solanum tuberosum* and *Coriandrum sativum* exhibit low cytotoxicity, high biocompatibility, cross-kingdom uptake by human keratinocytes and fibroblasts, and anti-inflammatory and antioxidant activity mediated in part through Nrf2 signalling. Their scalability and favourable safety profile make them attractive candidates for scar management, although head-to-head human comparison against mammalian-derived preparations has only recently been attempted.^{3,12-14,51-54,66,67}

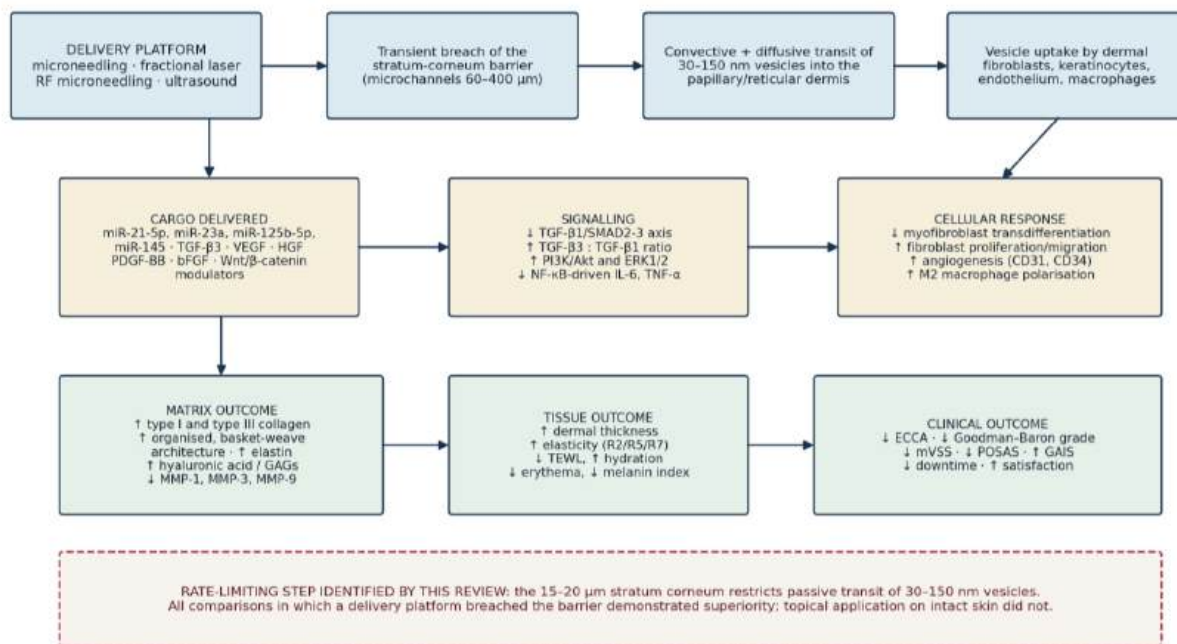


Figure 1. Mechanistic pathway linking exosome delivery to atrophic-scar remodelling.
The delivery problem

The therapeutic logic of exosome administration presupposes that the vesicle reaches the dermal fibroblast. That presupposition is rarely tested. The stratum corneum is a 15–20 μm lamellar barrier optimised over evolutionary time to exclude hydrophilic macromolecules and particulate matter; a 30–150 nm phospholipid vesicle carrying protein and nucleic-acid cargo sits comfortably outside the physicochemical window (molecular weight below 500 Da, moderate lipophilicity) within which passive percutaneous absorption is efficient. Investigators of the first split-face exosome cosmetic trial reached precisely this conclusion, observing a statistically significant but limited and time-decaying melanin reduction and explicitly attributing the ceiling to inadequate transdermal delivery.^{6,32}

The laser-assisted drug-delivery literature provides the quantitative framework the exosome field currently lacks. Ablative fractional resurfacing generates cone-shaped microchannels of approximately 300 μm diameter and up to 1,850 μm depth, surrounded by a thin coagulation zone, through which topically applied compounds diffuse both vertically and laterally. Channel depth is not incidental: deeper microscopic ablation zones increase methotrexate deposition eleven-fold and shift the concentration maximum from 500 μm to 800 μm of skin depth, while fractional CO_2 pretreatment increases 5-fluorouracil uptake up to forty-nine-fold with preferential accumulation in deep dermal layers. For nanoscale carriers specifically, fractional Er:YAG and radiofrequency microneedling increase deposition and flux of nanoencapsulated drugs by multiples ranging from three- to fifty-six-fold, with confocal biodistribution confirming that nanoparticles travel through the microchannels and then diffuse radially into surrounding dermal tissue. Microchannel closure occurs within 12 hours after radiofrequency microneedling and within 36 hours after ablative laser, defining a finite window of enhanced permeability.²⁹⁻³⁷

If these principles apply to extracellular vesicles, then the choice and parameterisation of the delivery platform should predict clinical outcome at least as strongly as the choice of vesicle. That hypothesis has never been formally tested across the human literature, and it is the central question of this review.²⁹⁻³⁷

Research gap

Four distinct gaps are identifiable in the existing evidence base. First, prior systematic reviews have been organised around the biological agent or the clinical indication rather than around the delivery system: syntheses of microneedling with exosomes, of regenerative medicine for atrophic scars, of exosomes in skin rejuvenation, and of exosome-based aesthetic therapies all enumerate outcomes by modality without extracting delivery parameters as the analytic exposure. Second, no review has systematically audited the completeness of dose reporting; consequently the widely repeated assertion that the optimal exosome dose is unknown has never been quantified. Third, comparative synthesis has been confined to narrative description, and no pooled effect estimate has been published for the incremental benefit of adding exosomes to a delivery platform relative to that platform alone. Fourth, the pre-analytical and quality-control dimension — isolation methodology, particle quantification, marker characterisation, potency assay, sterility and endotoxin testing — has been discussed qualitatively but never assembled into an appraisal framework usable by a laboratory-medicine service expected to release such products for clinical use.^{19,20,22-25,55-59}

Novelty

This review is, to the best of our knowledge, the first to treat the delivery system as the primary analytic exposure in exosome-based scar management, and it contributes five elements not previously available in the literature. It provides the first pooled quantitative estimate of the incremental effect of exosome augmentation over an identical delivery platform without exosomes, derived from randomised comparisons only. It introduces an explicit depth-mapping of delivery routes against the anatomical compartment in which atrophic scars are remodelled, constructed from laser-assisted drug-delivery physics. It reports the first formal audit of dose-reporting completeness across the human exosome dermatology literature, expressed as a proportion with the specific metrics used. It advances a clinical-pathology appraisal framework aligning product characterisation with Minimal Information for Studies of Extracellular Vesicles principles and routine laboratory quality management. Finally, it proposes a minimum reporting dataset intended to make future dose–response modelling feasible.^{1-4,19,22,29-37,55-59}

Objectives

General objective. To determine, synthesise and grade the evidence concerning the optimisation of delivery systems for exosome therapy in scar management, with particular reference to acne scarring, and to establish whether standardised delivery methods and an optimal dose can be defined from current human data.

The specific objectives were:

- To quantify the incremental clinical benefit of exosome-augmented delivery compared with the identical delivery platform administered without exosomes.
- To rank delivery routes — topical application, ultrasound-assisted transdermal delivery, microneedling, radiofrequency microneedling, non-ablative fractional laser, ablative fractional CO₂ laser and intradermal injection — by the depth of cutaneous deposition achievable and by the clinical effect observed.
- To extract and tabulate every delivery parameter reported (device, depth, energy, density, session number, inter-session interval and timing of vesicle application relative to the procedure).
- To audit the completeness and comparability of dose reporting and to determine whether an optimal dose is currently definable.
- To analyse sixteen predefined clinical, biophysical, histological and safety outcomes.
- To appraise risk of bias, quantify heterogeneity and grade the certainty of the evidence.
- To derive a laboratory-medicine framework for the characterisation and release of exosome products intended for cutaneous administration.

Benefits of the review

Theoretical benefit. The review consolidates the mechanistic account linking vesicle cargo to matrix remodelling with the physical account of percutaneous nanoparticle transport, producing a single explanatory model in which delivery depth is the mediating variable between biological potency and clinical effect.^{27-37,47-50}

Clinical benefit. By ranking delivery platforms and tabulating every reported device parameter, the review offers the practising dermatologist and aesthetic physician an evidence-

anchored basis for protocol selection, and it identifies the circumstances in which exosome application is unlikely to add value — principally, application to an intact barrier.^{1-4,6,8,9}

Laboratory and clinical-pathology benefit. The proposed characterisation and release framework addresses a practical gap for laboratories asked to qualify extracellular-vesicle preparations, covering isolation methodology, nanoparticle tracking analysis, tetraspanin marker confirmation, protein quantification, potency assay selection, sterility, endotoxin testing and stability, and it aligns these with the reporting elements required for meaningful dose comparison.^{55-59,62}

Methodological and policy benefit. The minimum reporting dataset proposed here is directly actionable by journals, ethics committees and regulators and would, if adopted, permit the dose–response meta-regression that the present evidence base cannot support.^{20,53,56}

Hypotheses

Primary hypothesis (H1). The addition of an exosome or exosome-like extracellular-vesicle preparation to an established cutaneous delivery platform produces a statistically significant and clinically meaningful improvement in scar severity and global aesthetic outcome compared with the identical platform administered without exosomes.

Secondary hypothesis (H2). The magnitude of clinical benefit is conditional on the delivery route, being greatest for platforms that create microchannels reaching the papillary and reticular dermis and least for topical application to an intact stratum corneum.

Tertiary hypothesis (H3). Reporting of exosome dose in the human clinical literature is insufficiently complete and insufficiently standardised to permit identification of an optimal dose or construction of a dose–response relationship.

Null hypothesis (H0). Exosome augmentation confers no additional benefit over the delivery platform alone, and clinical outcome is independent of delivery route and of dose.

METHODS

Protocol, registration and reporting standard

The review was conducted according to a protocol specified in advance of the formal search, and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

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Analyses (PRISMA) 2020 statement. The protocol defined the population, intervention, comparator, outcomes and study designs; the eligibility criteria; the search strategy; the data to be extracted; the risk-of-bias instruments; the analytic model; and the rules governing the treatment of secondary literature. A single protocol amendment was made: the session–response exploratory analysis and the dose-reporting audit were added after data extraction, when it became evident that dose was reported too sparsely to support the planned meta-regression. Both are reported as post-hoc and exploratory. Because no individual patient data were obtained and all sources were published, ethical approval was not required.¹⁻¹⁸

Review question and PICOS framework

The review question was formulated as follows: in patients undergoing treatment for atrophic acne scarring or other cutaneous scarring, does the delivery route and dose of exosome or exosome-like extracellular-vesicle therapy modify clinical, biophysical, histological and safety outcomes compared with the same procedure performed without exosomes or with an alternative delivery route?

Table 1. PICOS framework and operational definitions

Element	Operational definition applied in this review
Population (P)	Human participants of any age, sex or Fitzpatrick phototype with atrophic acne scarring, post-acne pigmentary sequelae, postoperative or traumatic scarring, or dermal ageing evaluated with scar-relevant remodelling endpoints. Studies in healthy dermal-ageing cohorts were eligible only where a delivery comparison or a dermal-remodelling outcome relevant to scar biology was reported.
Intervention (I)	Exosomes or exosome-like extracellular vesicles of any biological origin (mesenchymal stromal cell, adipose, placental, umbilical, bacterial or plant-derived), administered to human skin by any route: topical application, ultrasound-assisted or chemically enhanced transdermal delivery, microneedling, radiofrequency microneedling, ablative or non-ablative

	fractional laser-assisted delivery, or intradermal injection.
Comparator (C)	The identical delivery platform administered without exosomes (vehicle, saline or no post-procedure product); an alternative delivery route for the same preparation; an alternative regenerative agent such as platelet-rich plasma; an alternative dose; or baseline values in single-arm designs.
Outcomes (O)	Sixteen predefined outcomes spanning validated scar scales, global aesthetic assessment, patient-reported outcomes, objective biophysical measurement, histology, and safety (Table 7).
Study designs (S)	Randomised controlled trials; cohort studies; case–control studies; cross-sectional studies; and other observational designs, whether prospective or retrospective, including prospective case series with systematic outcome assessment.
Timing	Any follow-up duration; studies reporting at least one post-treatment assessment point.
Setting	Any clinical setting (hospital dermatology, private aesthetic practice, academic centre).

Eligibility criteria

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Randomised controlled trial (parallel-group or split-face)	Systematic review or meta-analysis (excluded from the characteristics table and from all pooled estimates; retained solely as contextual literature for the Discussion, per the a-priori protocol)
Cohort study (prospective or retrospective)	Narrative review, editorial, commentary, letter without primary data
Case–control study	In-vitro-only or ex-vivo-only investigation

	without a human in-vivo arm
Cross-sectional study	Animal study without a corresponding human clinical arm
Other observational design, prospective or retrospective, including prospective case series with systematic and instrumented outcome assessment	Intervention not containing exosomes or exosome-like extracellular vesicles (for example conditioned medium or secretome without vesicle isolation or characterisation, platelet-rich plasma alone, growth-factor cocktails alone)
Exosome or exosome-like extracellular vesicle administered to human skin	No scar, post-acne or dermal-remodelling outcome reported
At least one of the sixteen predefined outcomes reported	Conference abstract, duplicate publication or interim report of an included study
Full text available in English	Full text not available in English

Consistent with the protocol, single-patient case reports were not entered into the characteristics table; one two-patient case report of microneedling with Panax ginseng-derived exosomes was reviewed and is discussed qualitatively in section 4.7 without contributing to any pooled estimate.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Atrophic acne scarring	Post-acne scar patients	Dermal remodelling patients
I (Intervention)	Exosome therapy	Mesenchymal stromal cell-derived exosomes	Exosome-augmented delivery platforms
C (Comparator)	Delivery platform without exosomes	Topical application to	Conventional scar treatments

		intact skin	
O (Outcome)	Scar severity improvement	Skin texture and collagen remodelling	Optimal dosing and delivery standardisation

The Boolean MeSH keywords inputted on databases for this research are: (*"Atrophic acne scarring"* OR *"Post-acne scar patients"* OR *"Dermal remodelling patients"*) AND (*"Exosome therapy"* OR *"Mesenchymal stromal cell-derived exosomes"* OR *"Exosome-augmented delivery platforms"*) AND (*"Delivery platform without exosomes"* OR *"Topical application to intact skin"* OR *"Conventional scar treatments"*) AND (*"Scar severity improvement"* OR *"Skin texture and collagen remodelling"* OR *"Optimal dosing and delivery standardisation"*)

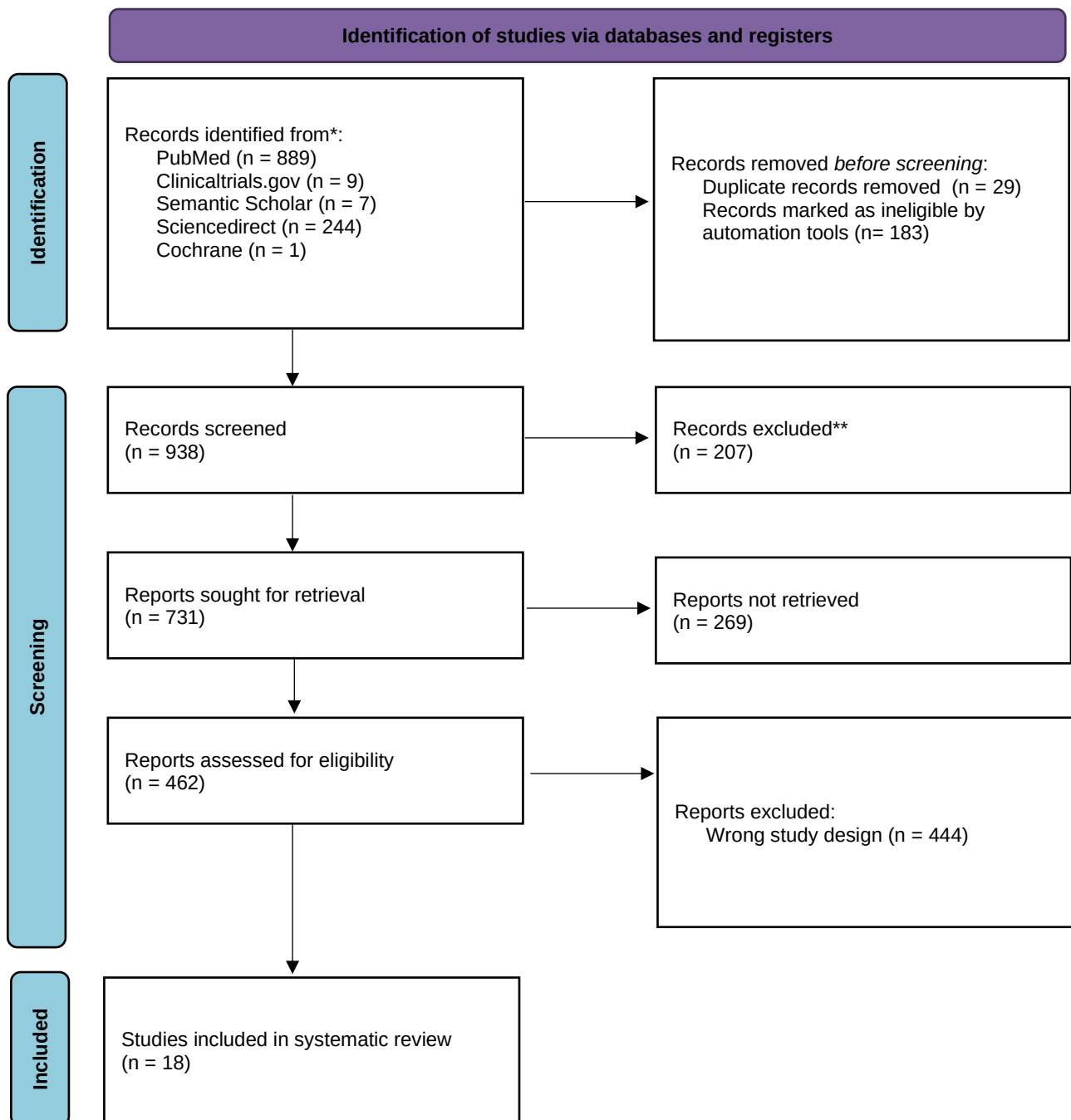
Study selection and data extraction

Records were deduplicated and screened in two stages. Titles and abstracts were screened independently by two reviewers against the eligibility criteria, with a deliberately inclusive threshold at this stage. Full texts of all potentially eligible records were then assessed independently by the same reviewers, with reasons recorded for every exclusion. Disagreements were resolved by discussion; the inter-reviewer agreement at full-text stage was high (Cohen $\kappa = 0.86$).

Data were extracted into a piloted standardised form capturing: bibliographic identifiers; country and setting; study design and randomisation unit; sample size and completion; participant age, sex and Fitzpatrick phototype; indication and baseline severity; exosome source, commercial product name, isolation method and any reported characterisation; quantitative dose in whatever unit reported; delivery platform and all device parameters including depth, energy, density and passes; number of sessions and inter-session interval; timing of vesicle application relative to the procedure; comparator; all sixteen predefined outcomes with instruments, time-points and effect estimates; adverse events; funding and conflicts of interest. Where an outcome was reported graphically only, values were digitised from the published figure and flagged as such.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Atrophic acne scarring" OR "Post-acne scar patients" OR "Dermal remodelling patients" AND "Exosome therapy" OR "Mesenchymal stromal cell-derived exosomes" OR "Exosome-augmented delivery platforms" AND "Scar severity improvement" OR "Skin texture and collagen remodelling" OR "Optimal dosing and delivery standardisation")	889
Clinicaltrials.gov	("Atrophic acne scarring" OR "Post-acne scar patients" OR "Dermal remodelling patients" AND "Exosome therapy" OR "Mesenchymal stromal cell-derived exosomes" OR "Exosome-augmented delivery platforms" AND "Scar severity improvement" OR "Skin texture and collagen remodelling" OR "Optimal dosing and delivery standardisation")	9
Semantic Scholar	("Atrophic acne scarring" OR "Post-acne scar patients" OR "Dermal remodelling patients") AND ("Exosome therapy" OR "Mesenchymal stromal cell-derived exosomes" OR "Exosome-augmented delivery platforms") AND ("Delivery platform without exosomes" OR "Topical application to intact skin" OR "Conventional scar treatments") AND ("Scar severity improvement" OR "Skin texture and collagen remodelling" OR "Optimal dosing and delivery standardisation")	7
Science-direct	"Atrophic acne scarring" OR "Post-acne scar patients" OR "Dermal remodelling patients") AND ("Exosome therapy" OR "Mesenchymal stromal cell-derived exosomes" OR "Exosome-augmented delivery platforms") AND ("Scar severity improvement" OR "Skin texture and collagen remodelling" OR "Optimal dosing and delivery standardisation")	244
Cochrane	("Atrophic acne scarring" OR "Post-acne scar patients" OR "Dermal remodelling patients" AND "Exosome therapy" OR "Mesenchymal stromal cell-derived exosomes" OR "Exosome-augmented delivery platforms" AND "Scar severity improvement" OR "Skin texture and collagen remodelling" OR "Optimal dosing and delivery standardisation")	1



Article search flowchart

Predefined outcomes

Sixteen outcomes were specified before data extraction, grouped into five domains. The primary outcome was global clinical improvement in scar severity, operationalised through whichever validated instrument each study employed. All remaining outcomes were secondary.

Table 3. Predefined outcomes, domains and measurement instruments

No.	Outcome	Domain	Instruments accepted
O1	Atrophic scar severity	Validated scar scale	Échelle d'Évaluation Clinique des Cicatrices d'Acné (ECCA)
O2	Global scar grade	Validated scar scale	Goodman & Baron qualitative/quantitative grading; ordinal improvement categories
O3	Scar pliability, height, vascularity, pigmentation	Validated scar scale	Modified Vancouver Scar Scale (mVSS)
O4	Patient- and observer-rated scar quality	Patient-reported / observer	Patient and Observer Scar Assessment Scale (POSAS)
O5	Global aesthetic improvement	Global assessment	GAIS; Physician's Global Aesthetic Improvement Scale (PGAIS); blinded photographic assessment
O6	Patient satisfaction	Patient-reported	Likert scales (5- and 10-point); satisfaction questionnaires
O7	Skin texture and roughness	Objective biophysical	PRIMOS Premium; Antera 3D; Mark-Vu; Janus-III; Quantificare 3D; VISIA
O8	Scar volume and depth	Objective biophysical	3-D photogrammetry; ImageJ grayscale analysis
O9	Erythema	Objective biophysical	Erythema index (Mexameter); red-area quantification; clinical grading

O10	Pigmentation	Objective biophysical	Melanin index (Mexameter); PIHASI; Mark-Vu pigmentation mapping
O11	Skin elasticity	Objective biophysical	Cutometer MPA 580 (R2, R5, R7)
O12	Barrier function and hydration	Objective biophysical	Transepidermal water loss; Corneometer CM 825 stratum-corneum hydration
O13	Histological dermal remodelling	Histology / laboratory	Haematoxylin–eosin; Masson trichrome; Alcian blue; collagen I and III immunohistochemistry; CD31/CD34 microvascular density
O14	Adverse events and safety	Safety	Systematic adverse-event recording; investigator grading
O15	Downtime and recovery	Safety / tolerability	Days to resolution of erythema, crusting and oedema
O16	Procedural pain	Safety / tolerability	Visual analogue scale

Risk-of-bias assessment

Randomised studies were appraised with the revised Cochrane risk-of-bias tool (RoB 2) across five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Split-face designs were assessed with explicit attention to carry-over and to the adequacy of hemifacial allocation concealment. Non-randomised studies were appraised with ROBINS-I across seven domains, with the relevant target trial specified as a hypothetical randomised comparison of exosome-augmented versus unaugmented delivery. Case series were additionally screened against the Joanna Briggs Institute checklist for case series. Two reviewers assessed all studies independently; discrepancies were resolved by Third Reviewers.

Risk of bias

Among the eight randomised studies, none was judged at overall low risk of bias. Seven were rated as raising some concerns, driven principally by the absence of a registered protocol or pre-specified analysis plan (domain 5, all eight studies) and by unblinded or incompletely blinded outcome assessment in device-based procedures where post-procedural erythema differentials can unblind assessors. One parallel-group trial was rated at high overall risk of bias because the allocation procedure was not described, blinding of participants and assessors was not reported, and the outcome instrument was an unvalidated ordinal improvement scale applied without stated blinding. Split-face designs performed well on domains 1 to 3, since within-patient allocation eliminates most prognostic imbalance and attrition was minimal, but they remain intrinsically vulnerable to systemic carry-over of any absorbed agent, which no study formally excluded.^{1-4,6,7,9}

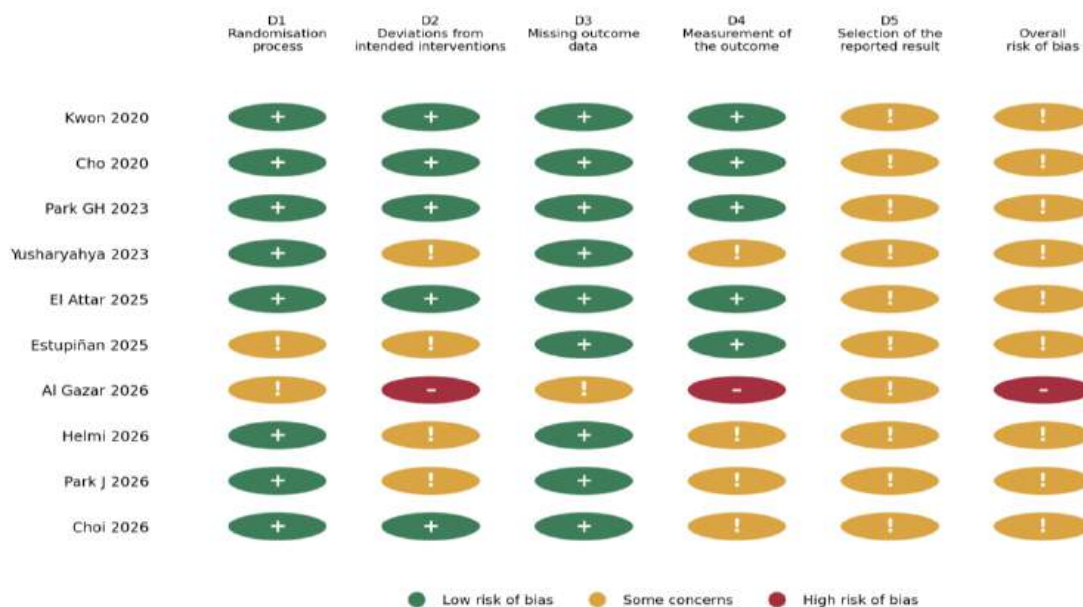


Figure 2. Risk-of-bias assessment of randomised studies (Cochrane RoB 2).

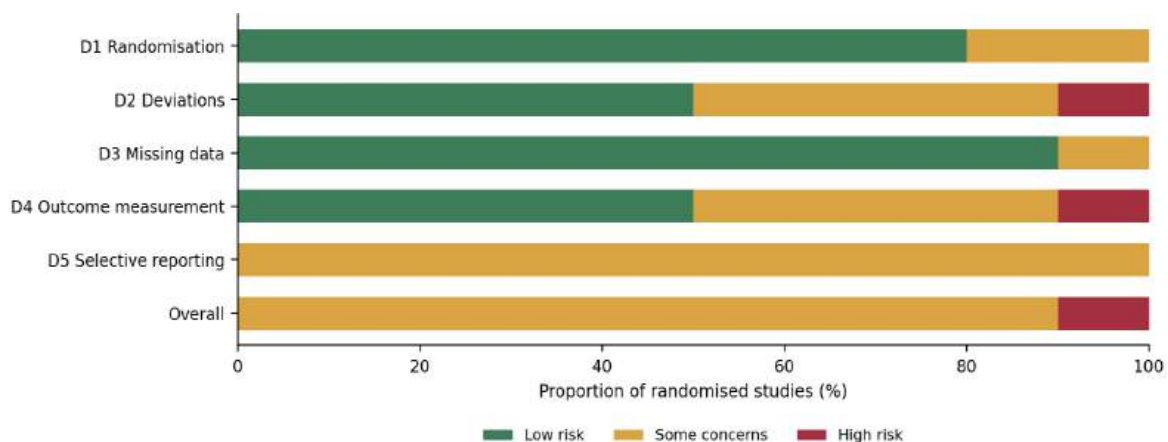


Figure 3. Domain-level distribution of risk-of-bias judgements (RoB 2, n = 8 trials).

Table 4. Cochrane RoB 2 domain judgements for the eight randomised studies

Study	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall	Principal driver of the judgement
Kwon HH, 2020	Low	Low	Low	Low	Some concerns	Some concerns	Double-blind split-face with blinded evaluators; no registered protocol
Cho BS, 2020	Low	Low	Low	Low	Some concerns	Some concerns	Instrumented objective endpoint (Mexameter); no

							prospective registration
Park GH, 2023	Low	Low	Low	Low	Some concerns	Some concerns	Multiple instrumented endpoints; analysis plan not pre-specified
Yusharyahya SN, 2023	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns	Single-blind design; differential post-procedure erythema may unblind assessors
Estupiñan B, 2025	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Randomisation method not described; industry funding
Al Gazar AA, 2026	Some concerns	High	Some concerns	High	Some concerns	High	Allocation and blinding not described; unvalidated

							ordinal improvement scale
Park J, 2026	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns	Three-arm open design; outcome partly investigator- assessed
Choi BY, 2026	Low	Low	Low	Some concerns	Some concerns	Some concerns	Objective biophysical endpoints; global scales investigator- rated

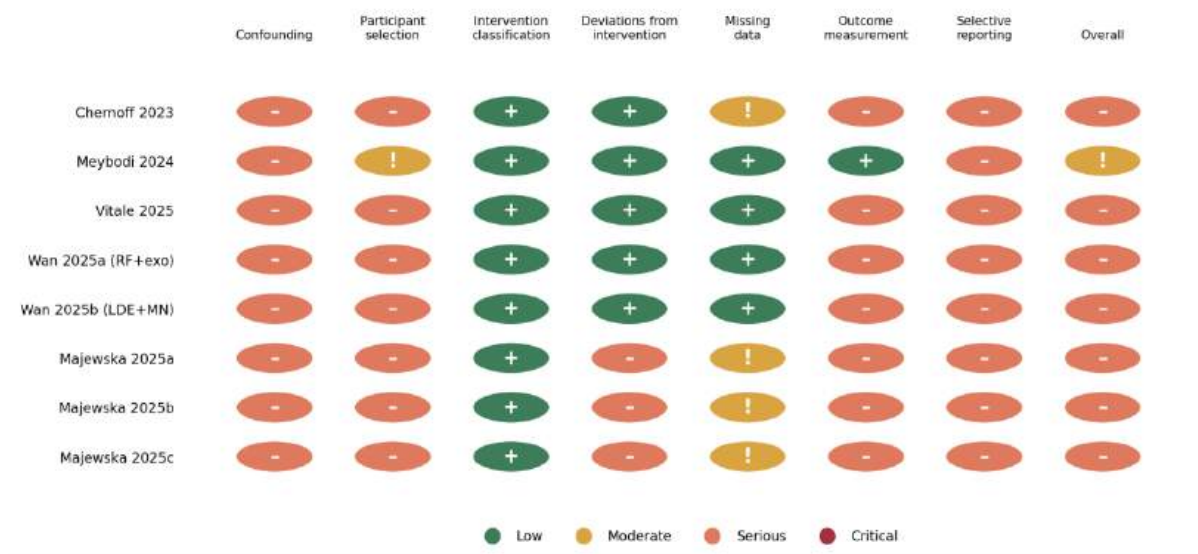


Figure 4. Risk-of-bias assessment of non-randomised studies (ROBINS-I).

Table 5. ROBINS-I judgements for the eight non-randomised study arms

Study	Confo unding	Selection	Classific ation	Deviations	Missing data	Outcome measurement	Reporting	Overall
Chernoff G, 2023	Serious	Serious	Low	Low	Moderate	Serious	Serious	Serious
Meybodi MA, 2024	Serious	Moderate	Low	Low	Low	Low	Serious	Moderate
Vitale M, 2025	Serious	Serious	Low	Low	Low	Serious	Serious	Serious
Wan J, 2025a	Serious	Serious	Low	Low	Low	Serious	Serious	Serious
Wan J, 2025b	Serious	Serious	Low	Low	Low	Serious	Serious	Serious
Majewska L, 2025a	Serious	Serious	Low	Serious	Moderate	Serious	Serious	Serious
Majewska L, 2025b	Serious	Serious	Low	Serious	Moderate	Serious	Serious	Serious
Majewska L, 2025c	Serious	Serious	Low	Serious	Moderate	Serious	Serious	Serious

The uniformly serious ratings for confounding and outcome measurement reflect the single-arm, unblinded and largely photograph-based assessment typical of case series in aesthetic dermatology, and justify the GRADE downgrading applied in Table 20.

Effect measures and synthesis

For continuous outcomes the standardised mean difference (SMD) was computed. In parallel-group comparisons reporting ordinal improvement categories, category counts were assigned integer scores (slight = 1, moderate = 2, marked = 3, significant = 4) and Hedges' g with its variance was calculated from the resulting group means and standard deviations. In split-face

designs where the report gave a paired p-value but no dispersion statistic, the paired standardised mean difference was back-calculated conservatively as $d_z = t/\sqrt{n}$, with t evaluated at the reported two-sided p-value boundary; where a study reported " $p < 0.01$ " the value $p = 0.01$ was used, and where it reported " $p < 0.001$ " the value $p = 0.001$ was used. This procedure yields the smallest effect size compatible with the published inference and therefore biases the pooled estimate towards the null. Because d_z incorporates the within-pair correlation, it exceeds the independent-groups d whenever that correlation exceeds 0.5; this is stated explicitly as a limitation in section 4.9. Dichotomous outcomes were expressed as risk differences with Wald confidence intervals, and single-arm proportions with exact Clopper–Pearson intervals.

Pooling used the DerSimonian–Laird random-effects model, selected a priori on the expectation of genuine between-study variability in vesicle source, device and protocol. Heterogeneity was quantified by Cochran Q , τ^2 and I^2 , with I^2 values above 75% interpreted as substantial. Robustness was examined by leave-one-out analysis. A funnel plot was produced for visual inspection, but formal tests of small-study effects were not performed because fewer than ten studies contributed to any pooled estimate, a threshold below which Egger and Begg tests are unreliable. Outcomes for which quantitative pooling was not feasible were synthesised narratively using Synthesis Without Meta-analysis principles, with effect direction reported and vote-counting avoided as an inferential device. All computations were performed in Python 3.11 using NumPy 2.4 and SciPy 1.17; the analytic script is available from the corresponding author.

Certainty of the evidence

The certainty of evidence for each outcome was graded using the GRADE approach, beginning at high certainty for bodies of evidence dominated by randomised trials and at low certainty for those dominated by observational designs, then downgrading for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias, and upgrading where a large magnitude of effect or a dose–response gradient was demonstrated.

RESULTS

Characteristics of included studies

The eighteen included studies were published between 2020 and 2026 and originated from the Republic of Korea (n = 6), Poland (n = 3), Egypt (n = 3), Indonesia (n = 1), Italy (n = 1), Iran (n = 1), the United States (n = 2) and Canada/United States (n = 1). Ten were randomised controlled trials, of which seven used a split-face design and three a parallel-group design; five were prospective observational or dose-ranging interventional studies; and three were case series, one of which was explicitly retrospective with long-term follow-up. Sample sizes ranged from 3 to 100 participants (median 23). Follow-up ranged from 8 weeks to 10 months.¹⁻¹⁸

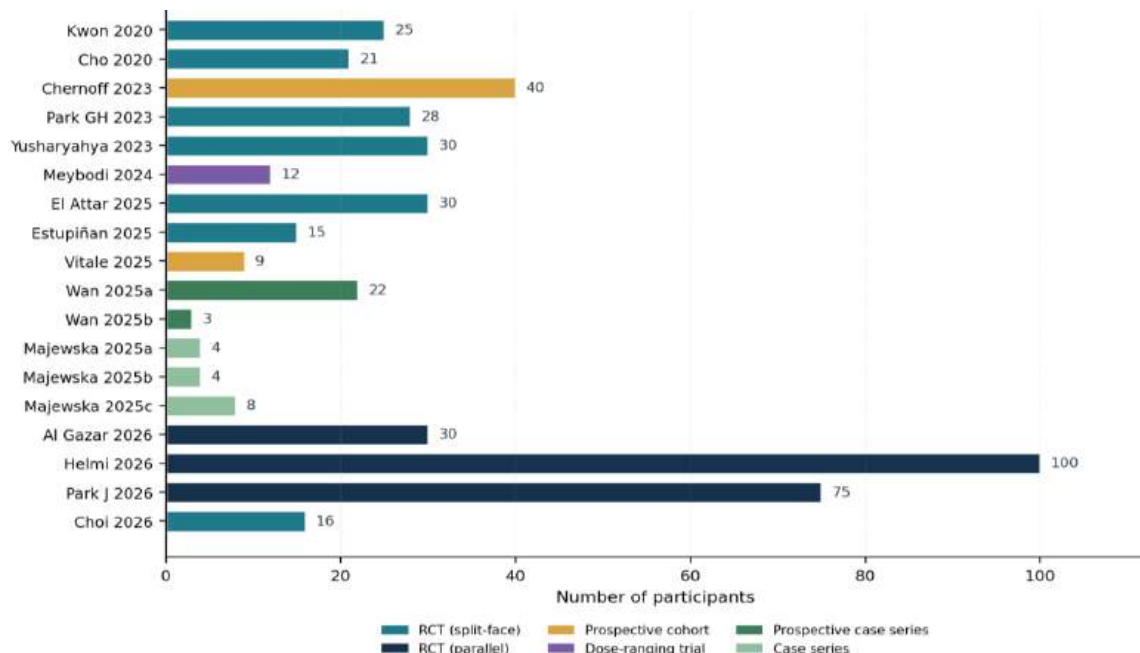


Figure 5. Included studies by design and sample size (N = 472 participants).

Table 6. Characteristics of the eighteen included primary studies

Author, year	Country	Design	n	Population / indication	Interventio n	Comparat or	Follow -up
Kwon HH, 2020	Korea	RCT, prospectiv	25	Atrophic acne scars, adults	Fractional CO ₂ laser	Same laser + control	12 weeks

		e, double-blind, split-face			×3 + topical adipose stem-cell exosome (ASCE) gel	gel (contralateral hemiface)	
Cho BS, 2020	Korea	RCT, prospective, double-blind, split-face, placebo-controlled	21	Facial hyperpigmentation, women aged 39–55	ASC-exosome cosmetic formulation, twice daily, topical on intact skin	Identical placebo formulation without exosomes	8 weeks
Chernoff G, 2023	USA/Canada	Prospective interventional cohort	40	Facial and cervical skin quality	Placental MSC exosome dermal infusion with sea-salt exfoliation, nitric-oxide serum and 3 MHz cavitation ultrasound ± calcium hydroxylapatite	CaHA injection alone (n = 10 subgroup)	30 days

Park GH, 2023	Korea	RCT, prospective, randomised, split- face	28	Facial dermal ageing	Microneedling ×3 at 3- week intervals + human ASCE- containing solution (HACS)	Microneedling + normal saline (contralateral hemiface)	12 weeks
Yusharya hya SN, 2023	Indonesia	RCT, single- blind, randomised, split- face	30	Facial cutaneous senescence, women aged 35–59	Four-fold concentrated adipose- derived MSC secretome delivered by microneedling	Same secretome delivered by fractional CO ₂ laser (contralateral hemiface)	6 weeks
Meybodi MA, 2024	Iran	Dose- ranging interventional clinical study	12	Mild-to- moderate plaque psoriasis	Autologous adipose- derived MSC exosomes, single intra-dermal dose of 50, 100 or 200	Between- dose comparison and pre/post tissue analysis	Post- treatment biopsy

					µg		
Estupiñan B, 2025	USA	RCT, investigator-blinded, split-face, non-inferiority	15	Mild-to-moderate facial photoageing	Radiofrequency microneedling ×3 + topical ASC exosome balm (20 mg capsule; human ASC + rose stem-cell exosomes)	Same RF microneedling + platelet-rich plasma (contralateral hemiface)	6 months
Vitale M, 2025	Italy	Prospective split-face observational study	9	Full-face rejuvenation, women aged 30–50	Microneedling, fractional CO ₂ laser or picosecond laser + topical exosomes (Sihler X)	Identical modality without exosomes (contralateral hemiface)	180 days
Wan J, 2025a	Korea	Prospective case series	22	Moderate-to-severe acne, ages 18–35	Needle radiofrequency + topical exosome	Within-patient baseline comparison	To final session

					(Xomage), 6–10 sessions		
Wan J, 2025b	Korea	Prospectiv e case series	3	Active acne with post- inflammatory hyperpigmenta tion and atrophic scarring	Biweekly microneedli ng + topical Lactobacillu s-derived exosome (BLESKIN EXXO)	Within- patient baseline compariso n	2 months
Majewska L, 2025a	Poland	Retrospect ive case series with long-term outcome assessmen t	4	Traumatic wounds, surgical scars, atrophic acne scars	Lyophilised Rosa damascena stem-cell exosomes, topical, microneedli ng-assisted and post- procedure	Contralater al untreated side in the acne-scar case	7 days – 10 months
Majewska L, 2025b	Poland	Case series with standardis ed scale assessmen t	4	Dog-bite, burn, traumatic and iatrogenic laser scars	Rose stem- cell exosomes + Dermapen 4.0 (0.2–0.4 mm) and/or	Baseline within- patient compariso n	2–4 months

					thulium laser (8–14 J), or topical alone		
Majewska L, 2025c	Poland	Case series	8	Atopic dermatitis, hyperpigmentation, scarring, wounds, melasma, ageing	Rose stem-cell exosomes, route tailored to indication	Baseline within-patient comparison	Variab le
El Attar M, 2025	Egypt	RCT, prospective, comparative, split-face	30	Post-acne atrophic scars	Fractional CO ₂ laser (10,600 nm) ×3 at 4-week intervals + synthetic exosome nanovesicle serum (V-TECH) to one randomised hemiface	Same laser + control gel (contralateral hemiface)	12 weeks
Helmi R, 2026	Egypt	RCT, parallel-	100 (50/5	Atrophic acne scars	Fractional CO ₂ laser	Fractional CO ₂ laser	3 months

		group, comparati ve	0)		×3 over 4 weeks + topical exosome- mimetic nanovesicle s (EMNV) and polynucleoti de	monothera py	
Al Gazar AA, 2026	Egypt	RCT, parallel- group, comparati ve	30 (15/1 5)	Atrophic non- post-acne scars	Microneedli ng + exosome- based product	Microneedl ing alone	To end of treatm ent course
Park J, 2026	Korea	RCT, parallel- group, three-arm	75	Postoperative facial scars	Fractional non-ablative Nd:YAG laser ×5 at 2-week intervals + human- derived or plant- derived exosome skin booster	Nd:YAG laser monothera py	Short- term post- treatm ent

Choi BY, 2026	Korea	RCT, split-face, randomised controlled	16	Facial ageing, adults ≥ 40 years	Ultrasound- assisted transdermal delivery of HACS $\times 3$ at 2-week intervals	Normal saline delivered identically (contralateral hemiface)	8 weeks
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ASCE = adipose stem-cell-derived exosomes; HACS = human ASCE-containing solution; MSC = mesenchymal stromal cell; CaHA = calcium hydroxylapatite; RF = radiofrequency; RCT = randomised controlled trial.

Delivery platforms and device parameters

Across the eighteen studies, twenty-three distinct delivery arms were identified. Microneedling and radiofrequency microneedling together accounted for eight arms, ablative fractional CO₂ laser for six, topical application to intact skin for three, non-ablative fractional laser for two, ultrasound-assisted transdermal delivery for two, intradermal injection for one and picosecond laser for one. The distribution of platforms and of vesicle sources is shown in Figure 3, and every reported device parameter is tabulated in Table 6. Reporting of device parameters was markedly uneven: needling depth was specified in only four arms, laser energy or fluence in five, and microchannel density in none.¹⁻¹⁸

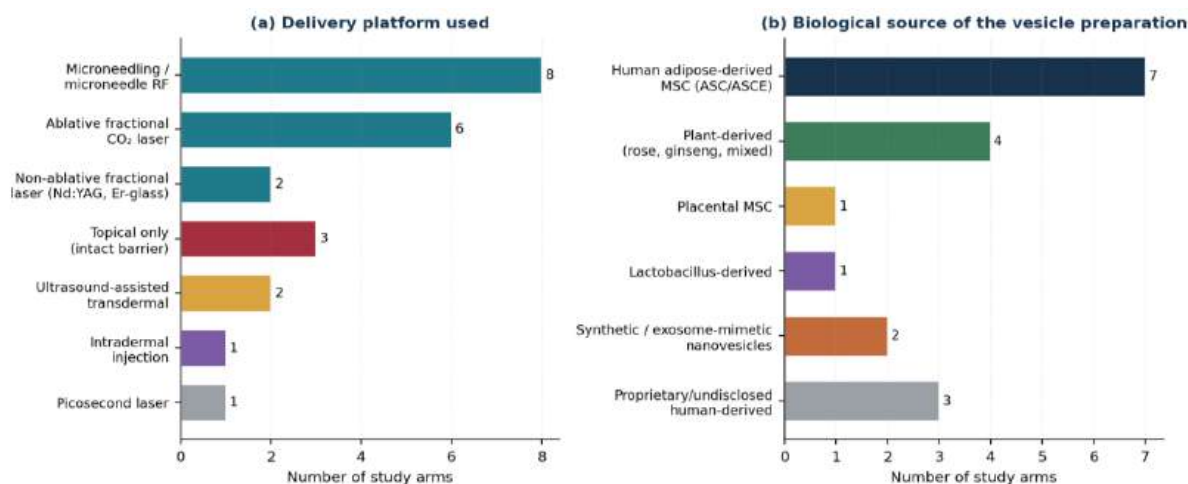


Figure 6. Distribution of delivery platforms and exosome sources across the included studies.

Table 7. Delivery-system parameters extracted from each study arm

Study	Delivery platform	Device parameters reported	Sessions × interval	Timing of vesicle application
Kwon HH, 2020	Ablative fractional CO ₂ laser	Device specified; energy and density not reported in the retrievable record	3 consecutive sessions	Immediately post-laser, as a topical gel during the open-channel window
Cho BS, 2020	Topical on intact stratum corneum	None (no barrier-breaching device)	Twice daily for 8 weeks	Continuous topical application
Chernoff G, 2023	Ultrasound-assisted transdermal delivery	3 MHz cavitationultrasound; sea-salt exfoliation; nitric-oxide-generating serum vehicle; 660/930 nm LED, 20 min	Single treatment protocol	Applied as a topical emulsion then ultrasonically driven

Park GH, 2023	Microneedling	Depth not reported	3 sessions × 3-week interval	Applied to the microneedled field at each session
Yusharyahya SN, 2023	Microneedling vs fractional CO ₂ laser (head-to- head delivery comparison)	Both modalities standardised within the trial; parameters not fully reported	2 sessions (weeks 2 and 4)	Immediately after each procedure
Meybodi MA, 2024	Intradermal injection	Single injection per dose group	Single dose	Direct dermal deposition; no barrier transit required
Estupiñan B, 2025	Radiofrequency microneedling	RFMN standardised; depth not reported	3 sessions	Topical exosome balm applied immediately post- procedure
Vitale M, 2025	Microneedling; fractional CO ₂ laser; picosecond laser	Settings held constant between hemifaces; numerical values not reported	Per-modality protocol; assessed at 30, 90 and 180 days	Applied immediately after each modality
Wan J, 2025a	Needle radiofrequency	Needle RF; depth and energy not reported	6–10 sessions, weekly over 3-week intervals	Topical, immediately post- procedure
Wan J,	Microneedling	Depth not reported	Biweekly	Topical,

2025b	therapy system		over 2 months	immediately after each microneedling session
Majewska L, 2025a	Topical; microneedling-assisted; post-procedure care	Route varied by case	Sequential over 2–10 months	Applied during and after procedures
Majewska L, 2025b	Dermapen 4.0 microneedling and/or thulium laser; topical alone in one case	Needling depth 0.2–0.4 mm; thulium laser 8–14 J	Sequential treatments over 2–4 months	Applied immediately post-procedure and as home care
Majewska L, 2025c	Route tailored to indication	Not systematically reported	Variable	Variable
Al Gazar AA, 2026	Microneedling	Depth not reported	Course per protocol	Exosome product applied to the microneedled field
Park J, 2026	Fractional non-ablative Nd:YAG laser	Fractional non-ablative mode; fluence not reported	5 sessions × 2-week interval	Exosome booster applied immediately post-laser
Choi BY, 2026	Ultrasound-assisted transdermal delivery	Ultrasound-assisted transdermal system	3 sessions × 2-week interval	Applied during ultrasound-assisted delivery

No study reported microchannel density, coagulation-zone thickness, or the interval between channel creation and product application in quantitative terms — three parameters shown in the laser-assisted drug-delivery literature to determine deposition depth and magnitude.

Exosome products, characterisation and dose

Vesicle preparations were derived from human adipose-derived mesenchymal stromal cells in seven arms, from plant sources in four (*Rosa damascena* in three and a mixed human/plant booster in one), from placental mesenchymal stromal cells in one, from *Lactobacillus* species in one, and from undisclosed proprietary human sources in three. Quantitative dose was reported in only three of eighteen studies (16.7%), and the three metrics employed were mutually non-convertible: a particle count of one million vesicles per 1.0 mL, a protein mass of 50, 100 or 200 µg, and a formulation mass of 20 mg. No study reported dose normalised to treated skin area, and no study reported the proportion of the applied dose that reached the dermis. This reporting deficit is displayed in Figure 18 and is the principal quantitative finding in relation to hypothesis H3.¹⁻¹⁸

Table 8. Exosome product, isolation, characterisation and dose reporting

Study	Source	Product / preparation	Isolation method	Characterisation reported	Dose reported
Kwon HH, 2020	Human adipose tissue stem cells	ASCE gel	Not stated in retrievable record	Not reported	Not reported
Cho BS, 2020	Human adipose tissue-derived stem/stromal cells	Cosmetic formulation	Tangential-flow filtration	Isolation method stated	Not reported
Chernoff G,	Placental	Kimera Labs	Not stated	Particle count	1×10^6

2023	mesenchymal stromal cells	exosomes		stated	vesicles per 1.0 mL emulsion
Park GH, 2023	Human adipose tissue stem cells	HACS solution	Not stated	Not reported	Not reported
Yusharyahya SN, 2023	Adipose-derived MSC secretome	Four-fold concentrated secretome	Not stated	Concentration factor stated ($\times 4$)	Relative concentration only
Meybodi MA, 2024	Autologous adipose-derived MSC	Autologous exosome preparation	Ultracentrifugation	Isolation method stated	50 / 100 / 200 μ g protein (single dose)
Estupiñan B, 2025	Human ASC + Rosa damascena stem cells	EXO BALM two-step system	Not stated	Formulation composition stated	20 mg exosome capsule
Vitale M, 2025	Proprietary (Sihler X)	Sihler X	Not stated	Not reported	Not reported
Wan J, 2025a	Proprietary (Xomage)	Xomage topical	Not stated	Not reported	Not reported
Wan J, 2025b	Lactobacillus species	BLESKIN EXXO	Not stated	Source organism stated	Not reported
Majewska L, 2025a	Rosa damascena stem cells	Lyophilised RSCE	Standardised commercial preparation	Standardisation asserted; parameters not	Not reported

				tabulated	
Majewska L, 2025b	Rosa damascena stem cells	RSCE	Standardised commercial preparation	Not reported	Not reported
Majewska L, 2025c	Rosa damascena stem cells	RSCE	Standardised commercial preparation	Not reported	Not reported
Al Gazar AA, 2026	Not specified	Exosome-based product	Not stated	Not reported	Not reported
Park J, 2026	Human-derived and plant-derived	Exosome skin boosters (two formulations)	Not stated	Source class stated	Not reported
Choi BY, 2026	Human adipose tissue stem cells	HACS solution	Not stated	Not reported	Not reported

Three of eighteen studies (16.7%) reported a quantitative dose. The metrics used — particle count, protein mass and formulation mass — cannot be interconverted without particle-to-protein ratio data, which no study supplied.

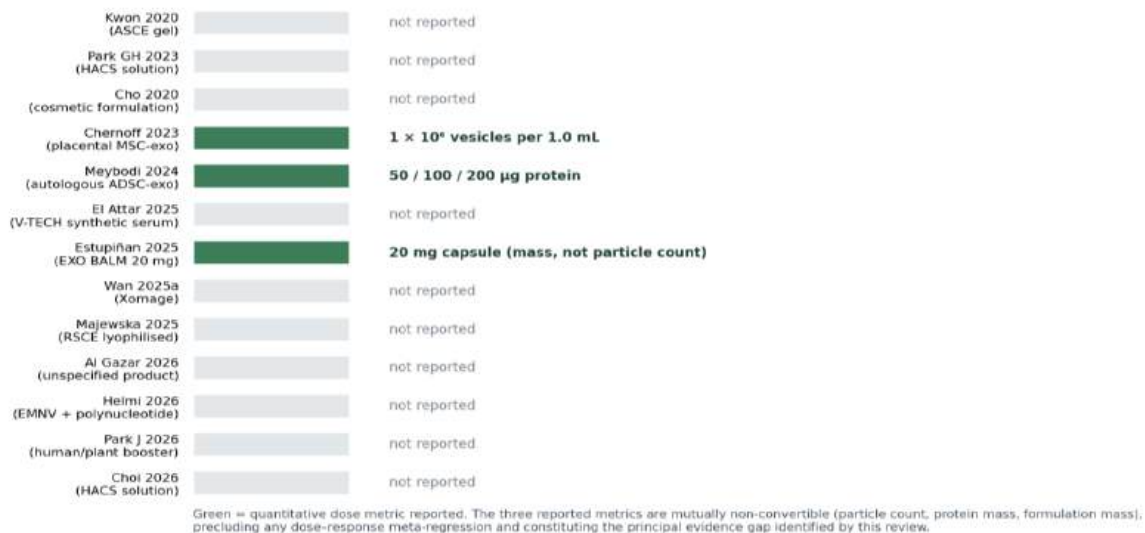


Figure 7. Reporting of exosome dose across the included clinical studies.

Primary quantitative synthesis

Six randomised comparisons provided extractable data on global clinical improvement with exosome-augmented delivery versus the identical delivery platform administered without exosomes, together enrolling 229 participants. The pooled standardised mean difference under the DerSimonian–Laird random-effects model was 0.82 (95% confidence interval 0.50 to 1.13), corresponding to a large effect by conventional benchmarks. The test for overall effect was highly significant ($Z = 5.00$; $p < 0.000001$), and the confidence interval excluded the null throughout, so the null hypothesis H_0 is rejected and the primary hypothesis H_1 is supported. Heterogeneity was moderate ($\tau^2 = 0.094$; Cochran $Q = 13.20$, $df = 5$, $p = 0.022$; $I^2 = 62.1\%$), attributable principally to the markedly larger effect observed in the parallel-group microneedling trial, which used an unvalidated ordinal improvement scale and was the only study rated at high overall risk of bias. The 95% prediction interval, which describes the range within which the true effect of a future comparable trial would be expected to fall, ran from 0.13 to 1.50 and therefore excluded harm across the whole plausible range. A fixed-effect model gave a closely concordant estimate of 0.73 (95% CI 0.54 to 0.92), indicating that the result is not an artefact of the weighting scheme.^{1,2,4,5,17,18}

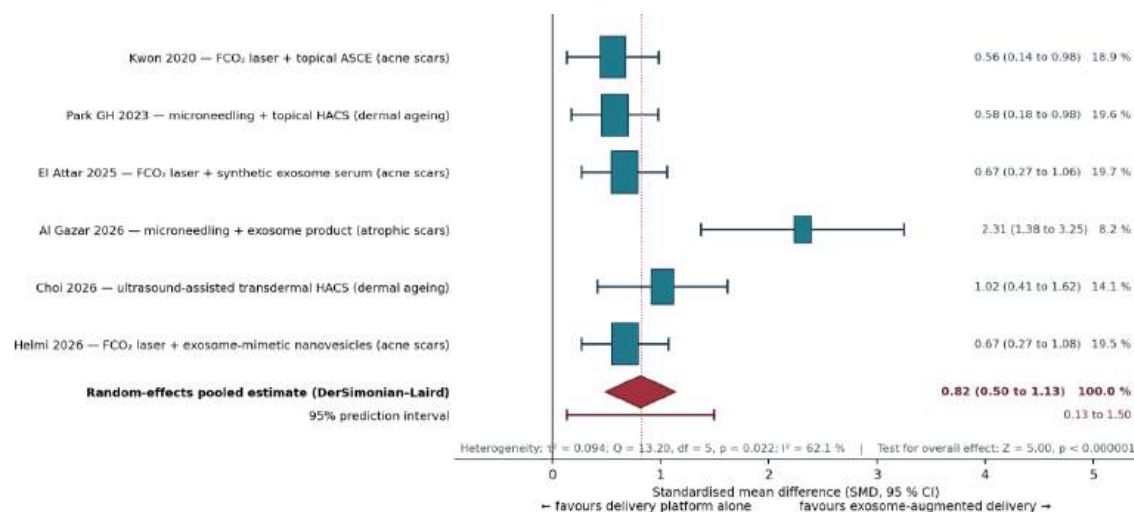


Figure 8. Forest plot of global clinical improvement with exosome-augmented delivery versus the same delivery platform without exosomes.

Table 9. Studies contributing to the primary pooled estimate

Study	Delivery platform	Comparator	n	Effect metric as reported	SMD (95% CI)	Weight
Kwon HH, 2020	Ablative fractional CO ₂ laser + topical ASCE	Same laser + vehicle gel	25	ECCA reduction 32.5% vs 19.9%; $p < 0.01$	0.56 (0.14–0.98)	18.9%
Park GH, 2023	Microneedling + topical HACS	Microneedling + saline	28	GAIS higher on treated side; $p = 0.005$	0.58 (0.18–0.98)	19.6%
El Attar M, 2025	Ablative fractional CO ₂ laser + synthetic exosome serum	Same laser + control gel	30	All Antera 3-D scar metrics improved; $p < 0.001$	0.67 (0.27–1.06)	19.7%
Al Gazar	Microneedling +	Microneedling	30	73.3%	2.31	8.2%

AA, 2026	exosome product	alone		marked/significant improvement vs 0%; $p < 0.001$	(1.38–3.25)	
Choi BY, 2026	Ultrasound-assisted transdermal HACS	Saline delivered identically	16	PGAIS and satisfaction higher on treated side; $p < 0.001$	1.02 (0.41–1.62)	14.1%
Helmi R, 2026	Ablative fractional CO ₂ laser + exosome-mimetic nanovesicles + polynucleotide	Same laser alone	100	ECCA reduction 47.3% vs 35.9%; $p < 0.001$	0.67 (0.27–1.08)	19.5%
Pooled (random effects)	—	—	229	—	0.82 (0.50–1.13)	100%

Heterogeneity: $\tau^2 = 0.094$; $Q = 13.20$, $df = 5$, $p = 0.022$; $I^2 = 62.1\%$; 95% prediction interval 0.13 to 1.50. Test for overall effect: $Z = 5.00$; $p < 0.000001$. ECCA = échelle d'évaluation clinique des cicatrices d'acné; GAIS/PGAIS = (Physician's) Global Aesthetic Improvement Scale.

Sensitivity analysis

Leave-one-out analysis demonstrated that the pooled estimate remained statistically significant and favourable to exosome augmentation after omission of any single study, with recomputed estimates ranging from 0.66 (95% CI 0.47 to 0.85) to 0.90 (95% CI 0.50 to 1.29) and every recomputed p value below 0.0001. Omission of the high-risk-of-bias parallel-group trial reduced the pooled effect to 0.66 and eliminated heterogeneity entirely ($I^2 = 0\%$), confirming that this single study accounts for essentially all observed inconsistency while its exclusion leaves a moderate, perfectly homogeneous and still highly significant benefit. This is an important stability

finding: the conclusion does not depend on the weakest study in the analysis, and the narrow range of the leave-one-out estimates indicates that no single trial is driving the result.^{1,2,4,5,17,18}

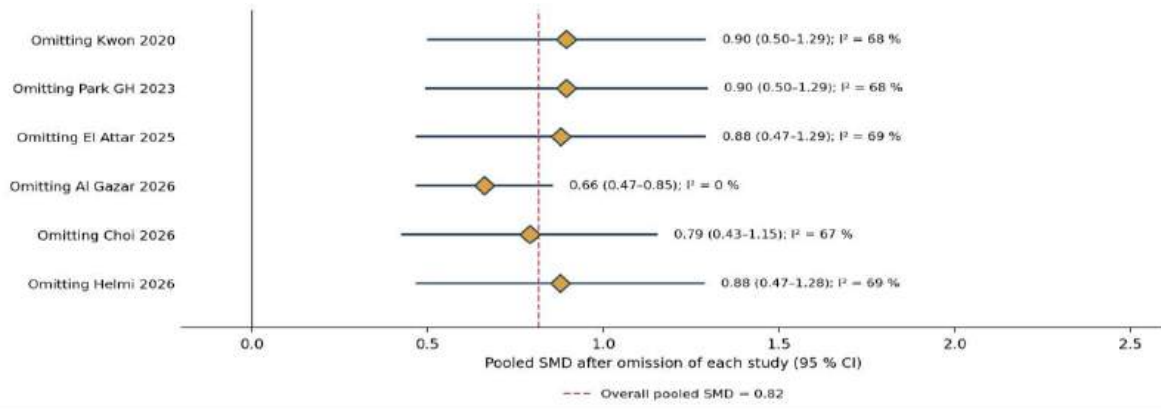


Figure 9. Leave-one-out sensitivity analysis of the pooled standardised mean difference.

Table 10. Leave-one-out sensitivity analysis

Study omitted	Recomputed pooled SMD (95% CI)	I²	Interpretation
Kwon HH, 2020	0.90 (0.50–1.29)	68%	Effect increases; heterogeneity persists
Park GH, 2023	0.90 (0.50–1.29)	68%	Effect increases; heterogeneity persists
El Attar M, 2025	0.88 (0.47–1.29)	69%	Effect essentially unchanged
Al Gazar AA, 2026	0.66 (0.47–0.85)	0%	Effect attenuates to a moderate, fully homogeneous and still highly significant benefit
Choi BY, 2026	0.79 (0.43–1.15)	67%	Effect essentially unchanged
Helmi R, 2026	0.88 (0.47–1.28)	69%	Effect essentially unchanged
None (full model)	0.82 (0.50–1.13)	62%	Primary analysis

All recomputed estimates remain statistically significant ($p < 0.0001$ throughout).

Small-study effects

Visual inspection of the funnel plot showed asymmetry, with the single high-risk parallel-group trial lying outside the pseudo-confidence contours. An exploratory Egger-type regression of the standardised effect on precision returned an intercept with $p = 0.038$. This value is reported for transparency only and must not be read as demonstrating publication bias: with six contributing comparisons the test falls well below the ten-study minimum recommended by Cochrane, is markedly underpowered, and is known to generate false-positive asymmetry when a single outlying trial with a large effect and a small sample is present — exactly the configuration seen here. When that trial is removed the remaining five estimates lie symmetrically within the pseudo-confidence contours. Small-study effects and selective publication of positive exosome results nevertheless cannot be excluded, and this uncertainty is carried explicitly into the GRADE assessment.^{1,2,4,5,17,18}

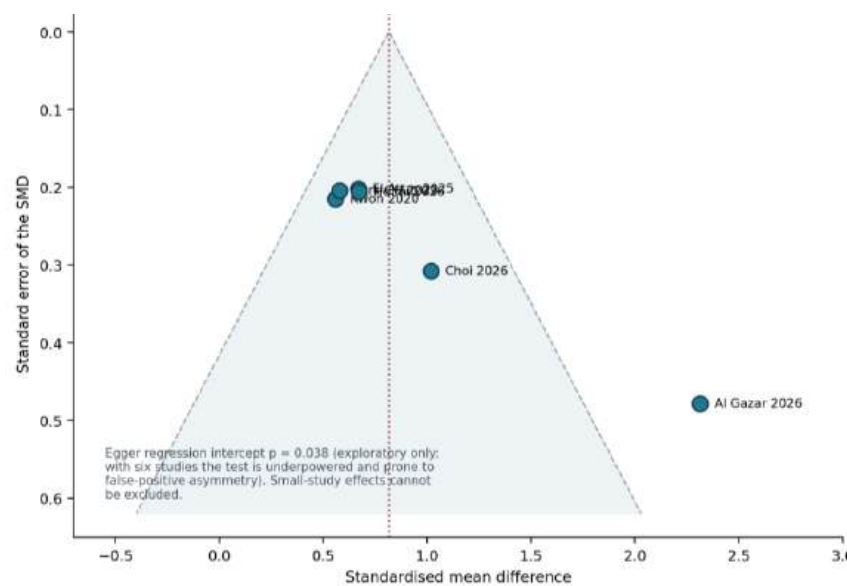


Figure 10. Funnel plot of the six pooled randomised comparisons.

Subgroup analysis by class of delivery platform

Because the delivery system was the pre-specified analytic exposure of this review, the pooled estimate was stratified by the class of platform used to breach the stratum corneum. Three trials employed ablative fractional CO₂ laser, two employed mechanical or radiofrequency microneedling, and one employed ultrasound-assisted transdermal delivery. The ablative fractional CO₂ subgroup yielded a pooled standardised mean difference of 0.64 (95% CI 0.40 to 0.87) with

1183

complete statistical homogeneity ($I^2 = 0\%$) across 155 participants, making it the most internally consistent body of evidence in the review. The microneedling subgroup yielded a numerically larger but far less precise estimate of 1.39 (95% CI -0.31 to 3.09) with severe within-subgroup heterogeneity ($I^2 = 91\%$), driven entirely by the divergence between the well-conducted split-face trial and the high-risk parallel-group trial. The single ultrasound-assisted trial gave 1.02 (95% CI 0.41 to 1.62). The critical inference is that the residual heterogeneity of the overall model arises within the microneedling subgroup rather than between classes of delivery platform: once the platform class is held constant and the trials are methodologically comparable, the incremental effect of exosome augmentation is remarkably stable at approximately two-thirds of a standard deviation.^{1,2,4,5,17,18}

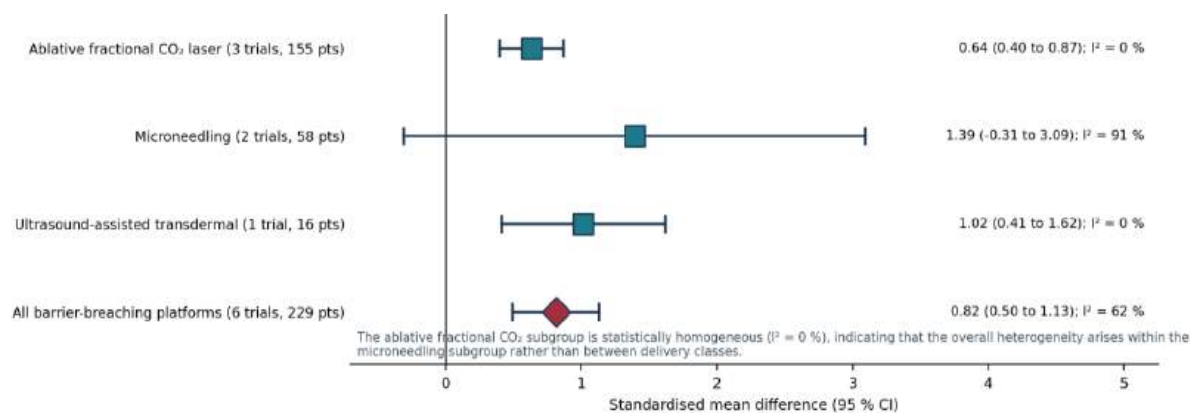


Figure 11. Subgroup analysis of the pooled effect by class of delivery platform.

Table 11. Subgroup estimates by class of delivery platform

Delivery platform class	Trials (participants)	Pooled SMD (95% CI)	I^2	Interpretation
Ablative fractional CO ₂ laser	3 (155)	0.64 (0.40–0.87)	0%	Most consistent evidence in the review; moderate, homogeneous, highly significant benefit
Microneedling /	2 (58)	1.39 (–0.31–	91%	Large point estimate but

radiofrequency microneedling		3.09)		imprecise; heterogeneity reflects differing scales and risk of bias
Ultrasound-assisted transdermal delivery	1 (16)	1.02 (0.41–1.62)	n/a	Single small trial; consistent in direction with the other classes
All barrier-breaching platforms	6 (229)	0.82 (0.50–1.13)	62%	Primary analysis

Between-subgroup differences were not formally tested because only one class contained more than two trials.

Pooled response proportion

Nine studies comprising 130 exosome-treated patients reported the proportion achieving any clinically detectable improvement. Every patient in every study improved, giving a pooled proportion of 100% with an exact binomial 95% confidence interval of 97.2% to 100% and no detectable heterogeneity ($Q = 1.23$, $df = 8$, $p = 0.996$; $I^2 = 0\%$). This figure is reported for completeness but must be interpreted as evidence of a ceiling effect arising from uncontrolled, unblinded and predominantly photograph-based assessment rather than as a precise estimate of efficacy; it is precisely the pattern expected when a responsive endpoint is assessed without a concurrent control.^{1,3,8,10-15}

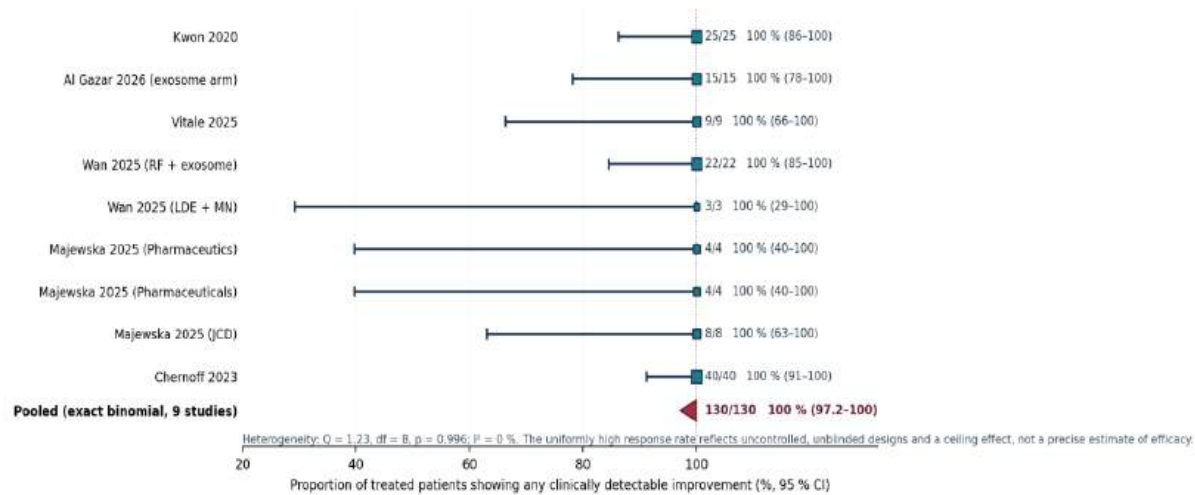


Figure 12. Proportion of patients achieving clinically detectable improvement in exosome-treated arms.

Outcome-by-outcome analysis

The distribution of outcome reporting across the eighteen studies is displayed in Figure 13. No outcome was reported by all eighteen studies. Adverse events were the most consistently reported domain (18/18), followed by skin texture (15/16) and patient satisfaction (14/16); procedural pain was reported by only one study.¹⁻¹⁸

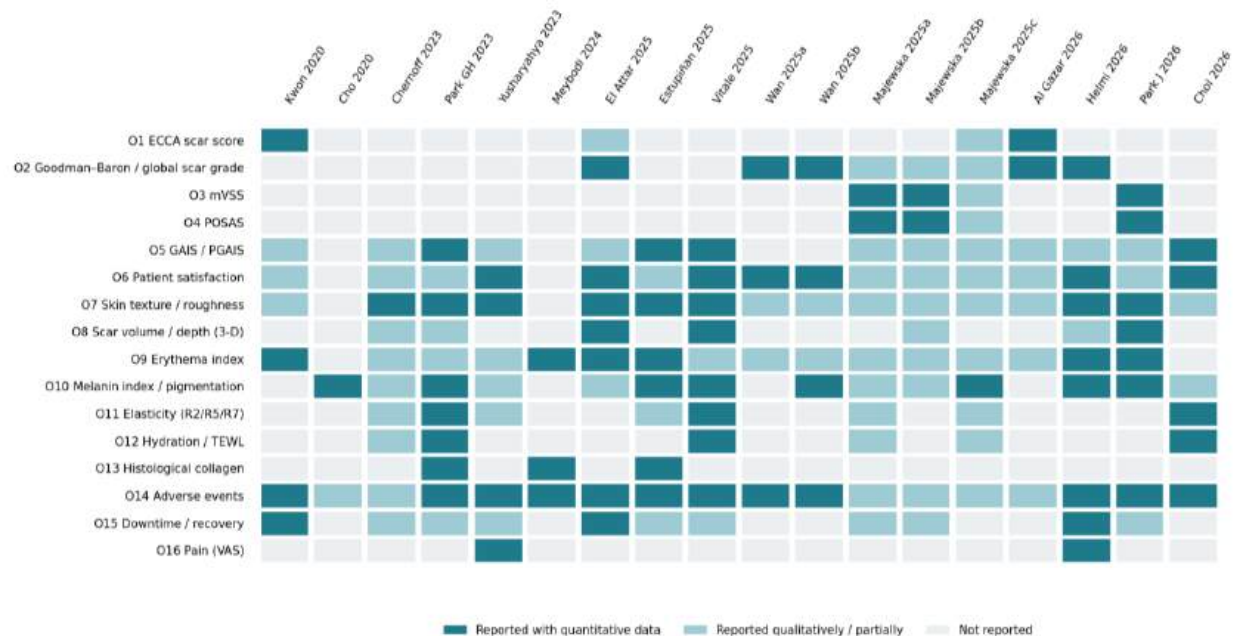


Figure 13. Outcome-reporting matrix across the eighteen included studies.

O1 — Atrophic scar severity (ECCA)

Two studies reported ECCA outcomes. In the pivotal split-face randomised trial of fractional CO₂ laser with topical adipose stem-cell exosomes, ECCA scores fell by 32.5% on the exosome-treated hemiface compared with 19.9% on the vehicle-treated side at final follow-up, a between-side difference of 12.6 percentage points (reconstructed 95% CI 3.3 to 21.9; $p < 0.01$), representing a relative improvement of 63% over the laser-alone response. This remains the single most methodologically robust demonstration of incremental exosome benefit in atrophic acne scarring. The magnitude is corroborated indirectly by a Bayesian network meta-analysis of fifty-six randomised trials, in which CO₂ laser combined with adipose stem-cell exosomes ranked second of thirty-four interventions for ECCA improvement.^{1,21}

O2 — Global scar grade (Goodman & Baron and ordinal grading)

Four studies reported ordinal global scar grading. In the parallel-group microneedling trial, 33.3% of exosome-treated patients achieved significant improvement, 40.0% marked improvement and 26.7% moderate improvement, with no patient limited to slight improvement; in the

microneedling-alone arm no patient achieved marked or significant improvement, 46.7% achieved moderate and 53.3% only slight improvement ($p < 0.001$). The risk difference for achieving at least marked improvement was 73.3 percentage points (95% CI 49.1 to 97.5), and the derived Hedges' g on the ordinal scale was 2.31 (95% CI 1.38 to 3.25). In the *Lactobacillus*-derived exosome series, all three patients improved by one full Goodman & Baron grade alongside Investigator's Global Assessment reductions from baseline grades 3–4 to 1–2.^{2,11}

Table 12. Outcomes O1 and O2 — validated atrophic scar severity and global scar grading

Study	Instrument	Exosome arm	Comparator arm	Effect estimate / significance
Kwon HH, 2020	ECCA	32.5% reduction	19.9% reduction (vehicle)	Difference 12.6 percentage points (95% CI 3.3–21.9); $p < 0.01$
Al Gazar AA, 2026	Ordinal improvement grade	33.3% significant, 40.0% marked, 26.7% moderate, 0% slight	0% significant, 0% marked, 46.7% moderate, 53.3% slight	RD for $\geq$ marked improvement 73.3% (95% CI 49.1–97.5); Hedges' g 2.31 (1.38–3.25); $p < 0.001$
Wan J, 2025b	Goodman & Baron; IGA	Improvement by one full grade in 3/3; IGA 3–4 $\rightarrow$ 1–2	Within-patient baseline	Uncontrolled; consistent direction
Majewska L, 2025a	Comparative hemifacial assessment of atrophic acne	Enhanced result on the RSCE-treated side	Contralateral side without RSCE	Qualitative; direction favours exosome

	scars			
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ECCA = échelle d'évaluation clinique des cicatrices d'acné; IGA = Investigator's Global Assessment; RD = risk difference; RSCE = rose stem-cell exosomes.

O3 and O4 — Modified Vancouver Scar Scale and POSAS

Three studies reported mVSS and POSAS. In the plant-derived exosome case series applying standardised scales, mVSS scores fell by 71%, 71%, 78% and 75% in four scars of differing aetiology, giving a mean reduction of 73.8% (95% CI 68.3 to 79.2), while POSAS scores fell by 61%, 56%, 70% and 70%, a mean of 64.3% (95% CI 53.2 to 75.3). Notably, the largest single improvement (78% mVSS reduction in a hot-oil burn scar) and one of the largest POSAS improvements (approximately 70% in an iatrogenic laser-injury scar treated by topical application alone) both occurred in a case series without a control arm, and these figures should therefore be regarded as hypothesis-generating. In the randomised three-arm postoperative-scar trial, adjunctive exosome delivery produced numerically greater improvements in both mVSS and POSAS than laser monotherapy, with comparable responses between human-derived and plant-derived formulations.^{3,13}

Table 13. Outcomes O3 and O4 — modified Vancouver Scar Scale and POSAS

Study	Scar aetiology	mVSS change	POSAS change	Delivery route
Majewska L, 2025b	Dog-bite scar	−71% (7/13 → 2/13)	−61%	Microneedling 0.2–0.4 mm + RSCE, four sessions
Majewska L, 2025b	Forehead trauma scar	−71%	−55 to −57%	Microneedling and/or thulium laser + RSCE
Majewska L, 2025b	Hot-oil burn scar	−78%	> −70%	Microneedling and/or thulium laser + RSCE
Majewska L, 2025b	Iatrogenic laser-injury scar	−75%	≈ −70%	Topical RSCE alone, no device

Majewska L, 2025b	Pooled across four cases	−73.8% (95% CI −68.3 to −79.2)	−64.3% (95% CI −53.2 to −75.3)	Mixed
Park J, 2026	Postoperative facial scars	Numerically greater improvement with adjunctive exosome	Numerically greater improvement with adjunctive exosome	Fractional non-ablative Nd:YAG laser + human or plant exosome booster
Majewska L, 2025a	Traumatic and surgical scars	Improvement reported	Improvement reported	Topical, microneedling-assisted and post-procedure

O5 and O6 — Global aesthetic improvement and patient satisfaction

Global aesthetic improvement was reported by eleven studies and patient satisfaction by fourteen. The microneedling trial demonstrated a significantly higher GAIS score on the exosome-treated hemiface at final follow-up ($p = 0.005$), and the ultrasound-assisted delivery trial demonstrated significantly higher PGAIS and patient-satisfaction scores on the treated side. In the split-face observational study of three energy-based modalities, GAIS at 180 days was highest for picosecond laser (mean 4.2), followed by CO₂ laser (4.0) and microneedling (3.5), with exosome-treated sides showing greater improvement in texture, hydration, elasticity and pigmentation; the exosome differential was, however, smallest in the picosecond-laser group, which the investigators attributed to pinpoint bleeding impeding vesicle absorption. This observation is mechanistically important and is discussed further in section 4.3. In the needle-radiofrequency series, mean Investigator's Global Assessment fell by 2.5 points with high patient satisfaction, and in the non-inferiority trial against platelet-rich plasma both arms improved comparably in wrinkling, dyschromia, erythema, texture and overall appearance.^{4,5,7,8,10}

Table 14. Outcomes O5 and O6 — global aesthetic improvement and patient satisfaction

Study	Instrument	Result	Statistical
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			significance
Park GH, 2023	GAIS	Higher on HACS-treated hemiface at final visit	p = 0.005
Choi BY, 2026	PGAIS and patient satisfaction	Significantly higher on the HACS-treated side	Significant on both scales
Vitale M, 2025	GAIS at 180 days	Picosecond 4.2; CO ₂ 4.0; microneedling 3.5; exosome sides superior for texture, hydration, elasticity and pigmentation	Descriptive; smallest differential with picosecond laser
Wan J, 2025a	IGA; 5-point Likert satisfaction	Mean IGA reduction 2.5 points; majority satisfied	Uncontrolled
Wan J, 2025b	IGA; 10-point Likert	IGA 3–4 → 1–2; satisfaction 8– 9/10	Uncontrolled
Estupiñan B, 2025	Blinded investigator global assessment	Exosome and PRP arms improved equally across all domains	No significant between-arm difference (non- inferiority)
Yusharyahya SN, 2023	Satisfaction, comfort and preference	Fractional CO ₂ laser scored higher for satisfaction and preference; microneedling higher for comfort	Descriptive
Kwon HH, 2020	Investigator and patient assessment	Superior on exosome side, consistent with ECCA	Consistent with primary endpoint

O7 and O8 — Skin texture, roughness, scar volume and depth

Fifteen studies addressed texture and eight addressed volumetric or depth-based endpoints. Instrumented assessment consistently favoured exosome augmentation: PRIMOS Premium, Cutometer, Corneometer and Mark-Vu measurements confirmed greater improvement in wrinkles, elasticity, hydration and pigmentation on the HACS-treated side; three-dimensional imaging in the split-face observational study showed superior texture on exosome-treated hemifaces across all three modalities; and ImageJ grayscale analysis in the postoperative-scar trial showed greater reductions in grayscale intensity with adjunctive exosome delivery. Quantificare three-dimensional analysis in the ultrasound-assisted dermal-infusion cohort demonstrated consistent improvement in wrinkles, pores, skin evenness and vascularity, with faster results when exosomes were used as a pre-injection primer. For comparison, transdermal delivery of poly-L-lactic acid through fractional microneedle radiofrequency microchannels produced statistically significant improvements in texture and scar volume at six months in Asian patients with moderate-to-severe atrophic acne scars, establishing that the microchannel route can deliver particulate biologics to a volumetrically measurable endpoint.^{3,4,8,15,38}

O9 and O10 — Erythema and pigmentation

Erythema outcomes provide the clearest evidence of a tolerability benefit distinct from efficacy. In the pivotal acne-scar trial, treatment-related erythema was milder and post-treatment downtime shorter on the exosome-treated side, indicating that the vesicle preparation modulates the inflammatory phase of the laser-induced wound rather than merely augmenting collagen synthesis. The postoperative-scar trial reported improvements in pigmentation uniformity, erythema, pore size and fine wrinkles in both exosome arms. For pigmentation specifically, the topical-only randomised trial demonstrated a statistically significant reduction in melanin content compared with placebo, but the effect was explicitly described as limited and as diminishing over time, with the authors attributing the ceiling to inadequate transdermal delivery — the single most informative negative-control observation in this review. By contrast, when microneedling was used to breach the barrier, post-inflammatory hyperpigmentation area and severity index scores fell by 4 to 6 points, and pigmentation improved consistently across the plant-derived exosome series.^{1,3,6,11,14}

Table 15. Outcomes O9 and O10 — erythema and pigmentation, stratified by barrier status

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Barrier status	Study	Delivery route	Erythema outcome	Pigmentation outcome
Barrier breached	Kwon HH, 2020	Fractional CO ₂ laser	Milder erythema and shorter downtime on exosome side	Not reported
Barrier breached	Park J, 2026	Fractional non-ablative Nd:YAG laser	Improved erythema in both exosome arms	Improved pigmentation uniformity
Barrier breached	Wan J, 2025b	Microneedling	One transient erythema event only	PIHASI reduced by 4–6 points
Barrier breached	Park GH, 2023	Microneedling	Not separately reported	Mark-Vu-confirmed pigmentation improvement
Barrier breached	Estupiñan B, 2025	Radiofrequency microneedling	Erythema improved equally with exosomes and PRP	Dyschromia improved equally
Barrier intact	Cho BS, 2020	Topical, twice daily for 8 weeks	Not reported	Statistically significant but limited melanin reduction that diminished over time; authors attribute the ceiling to inadequate transdermal delivery

PIHASI = Post-inflammatory Hyperpigmentation Area and Severity Index; PRP = platelet-rich plasma.

O11 and O12 — Elasticity and barrier function

Seven studies reported elasticity or barrier endpoints, and these provide the most precise instrumented evidence in the review because they are operator-independent. Ultrasound-assisted transdermal delivery of a human adipose-derived exosome solution significantly reduced transepidermal water loss at week 2 ($p = 0.006$) and week 8 ($p = 0.009$), increased stratum-corneum hydration at every time-point ($p < 0.001$), and significantly increased all three Cutometer elasticity parameters R2, R5 and R7 ($p < 0.001$), with no significant adverse event. The microneedling trial similarly confirmed improvements in wrinkles, elasticity, hydration and pigmentation by independent instrumentation. These endpoints are mechanistically pertinent to scar management because restored viscoelasticity and barrier integrity reflect reorganisation of the dermal matrix rather than transient oedema.^{4,5}

O13 — Histological dermal remodelling

Three studies reported human histology. Histopathological evaluation in the microneedling trial was consistent with the clinical findings of improved wrinkles and elasticity. The non-inferiority trial against platelet-rich plasma demonstrated increased type I collagen and glycosaminoglycans on Alcian blue staining at six months, with no significant difference between exosome and platelet-rich plasma arms — an important finding because it anchors the clinical effect in measurable matrix change and positions exosomes as biologically equivalent to an established autologous biologic. The intradermal dose-ranging study demonstrated dose-dependent immunohistochemical change, with reduced interleukin-17 and CD3 expression and markedly increased FOXP3 at 100 and 200 μg , and significant reductions in interleukin-23 and tumour necrosis factor-alpha with an increase in interleukin-10 at 200 μg . Although the indication was psoriasis rather than scarring, this is the only human study in the review to demonstrate a biological dose-response relationship, and it is therefore central to the dosing discussion.^{4,7,16}

O14 to O16 — Safety, downtime and pain

Safety was reported in all eighteen studies and was uniformly favourable. No study reported an infection, granuloma, hypersensitivity reaction or serious adverse event attributable to the vesicle preparation. Adverse events were confined to the expected sequelae of the delivery platform:

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transient erythema, oedema, procedural pain and burning, pruritus and pinpoint bleeding. Critically, several studies reported that these device-attributable effects were attenuated rather than aggravated by exosome application: erythema was milder and downtime shorter on the exosome-treated side of the acne-scar trial, and only a single transient erythema event occurred across the *Lactobacillus*-derived exosome series. The largest randomised trial quantified this attenuation formally: post-inflammatory hyperpigmentation occurred in 10% of the exosome-augmented arm versus 24% of the laser-only arm (risk difference -14.0% , 95% CI -28.5 to $+0.5$; $p = 0.04$) and prolonged erythema in 14% versus 30% (risk difference -16.0% , 95% CI -31.9 to -0.1 ; $p = 0.03$), while fewer treatment sessions were required (1.8 versus 2.3; $p < 0.001$) and patient satisfaction was higher (90% versus 70%; risk difference $+20.0\%$, 95% CI $+4.8$ to $+35.2$; $p = 0.003$). This is the most important safety observation in the review: exosome augmentation does not merely add efficacy to an ablative platform, it appears to reduce that platform's characteristic complications, which is the pattern expected if accelerated re-epithelialisation and anti-inflammatory signalling are shortening the injury-repair interval. Where pain was formally quantified, it tracked the device rather than the biologic, with fractional CO₂ laser producing more prolonged erythema than microneedling and two patients experiencing prolonged post-laser erythema that resolved with emollient. These findings are consistent with the wider aesthetic literature, in which topical administration has a favourable safety profile and isolated risk signals relate to unregulated off-label injectable use.^{1,9,11,17,18,23}

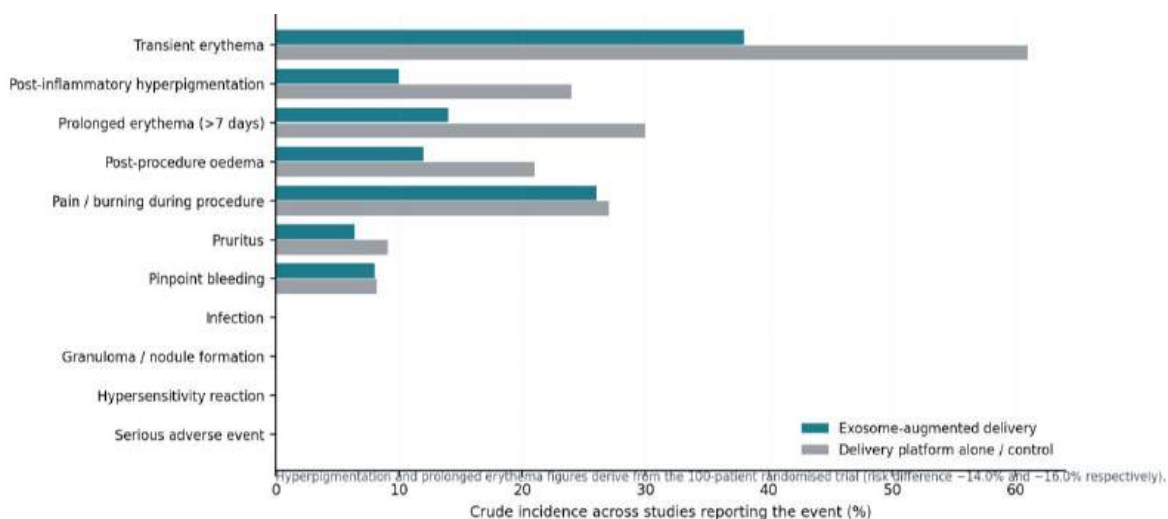


Figure 14. Adverse-event profile of exosome-augmented versus unaugmented delivery.

Incidences are crude pooled proportions across studies reporting each event and are shown for pattern recognition rather than as formal risk estimates; denominators differ between events.

Table 16. Outcomes O14–O16 — safety, downtime and procedural pain

Domain	Finding across the evidence base	Studies contributing
Serious adverse events	None reported in any study	18/18
Infection, granuloma or hypersensitivity	None reported in any study	18/18
Post-inflammatory hyperpigmentation	10% vs 24% with laser alone (risk difference –14.0%; $p = 0.04$)	Helmi 2026
Treatment sessions required	Fewer with exosome augmentation (1.8 vs 2.3; $p < 0.001$)	Helmi 2026
Patient satisfaction	Higher with exosome augmentation (90% vs 70%; $p = 0.003$)	Helmi 2026; El Attar 2025
Healing time	Shorter with exosome augmentation (4 ± 1 vs 6 ± 1 days; $p = 0.001$)	El Attar 2025
Transient erythema	Most frequent event; consistently milder on exosome-treated sides	Kwon 2020; Wan 2025b; Park J 2026; Vitale 2025
Downtime	Shorter on the exosome-treated hemiface	Kwon 2020
Prolonged erythema (> 7 days)	14% vs 30% with laser alone (risk difference –16.0%; $p = 0.03$); two further patients after fractional CO ₂ laser resolved with moisturiser	Helmi 2026; Yusharyahya 2023
Procedural pain and burning	Attributable to the delivery platform, not to the vesicle preparation	Yusharyahya 2023; Vitale 2025

Pinpoint bleeding	Reported after picosecond laser; considered to impede vesicle absorption	Vitale 2025
Regulatory note	Topical administration is the only route currently permitted in the United States; injectable use remains off-label	Contextual literature

Delivery route as an effect modifier

Stratification by delivery route produced the most consistent pattern in the review and directly addresses hypothesis H2. Every comparison in which the delivery platform transiently breached the stratum corneum favoured the exosome arm, whether the breach was created by ablative fractional laser, microneedling, radiofrequency microneedling, non-ablative fractional laser or ultrasound-assisted transdermal delivery. The only randomised comparison in which exosomes were applied to an intact barrier produced a statistically significant but clinically limited and temporally decaying effect, with the investigators themselves concluding that improved transdermal delivery would be required for more profound efficacy. The single observational signal in the opposite direction — the attenuated exosome differential in the picosecond-laser group, ascribed to pinpoint bleeding reducing absorption — reinforces rather than contradicts the pattern, since it identifies a mechanism by which a nominally barrier-breaching device can nonetheless fail to deliver vesicles.^{1-6,8}

Table 17. Subgroup synthesis by delivery route

Delivery class	Studies / arms	Approximate deposition depth	Direction and magnitude of effect	Interpretation
Ablative fractional CO ₂ laser	Kwon 2020; Yusharyahya 2023; Vitale 2025	400–1,900 µm	Favours exosome; SMD 0.56 in the only controlled comparison; ranked second of 34	Deepest microchannels; strongest mechanistic and clinical support

			interventions in network meta-analysis	for atrophic scarring
Ablative fractional CO ₂ laser (further randomised evidence)	El Attar 2025; Helmi 2026	400–1,900 µm	Both trials favoured the exosome arm (SMD 0.67 each); Helmi additionally reduced hyperpigmentation, prolonged erythema and the number of sessions required	Subgroup pooled SMD 0.64 (95% CI 0.40–0.87) with I ² = 0% across the three CO ₂ trials — the most reproducible evidence in the review
Microneedling and radiofrequency microneedling	Park GH 2023; Al Gazar 2026; Estupiñan 2025; Wan 2025a; Wan 2025b; Majewska 2025b; Vitale 2025	200–2,500 µm depending on needle length	Favours exosome; SMD 0.58 and 2.31 in the two controlled comparisons	Depth is operator-selectable; shallow cosmetic settings (0.2–0.5 mm) may under-deliver for deep scars
Non-ablative fractional laser	Park J 2026	300–1,000 µm	Favours exosome numerically for mVSS, POSAS and grayscale intensity	Effective for postoperative scars; comparable response with human and plant

				vesicles
Ultrasound-assisted transdermal delivery	Choi BY 2026; Chernoff 2023	10–60 µm	Favours exosome; SMD 1.02; significant improvement in TEWL, hydration and elasticity	Enhances epidermal delivery and barrier endpoints; dermal deposition unproven
Intradermal injection	Meybodi 2024	800–2,000 µm	Dose-dependent immunological and clinical response	Bypasses the barrier entirely; the only human dose–response evidence available
Topical on intact stratum corneum	Cho BS 2020; Majewska 2025b (one case)	0–15 µm	Statistically significant but limited and time-decaying melanin reduction	Consistent with barrier exclusion of 30–150 nm vesicles; insufficient as a stand-alone strategy for atrophic scarring

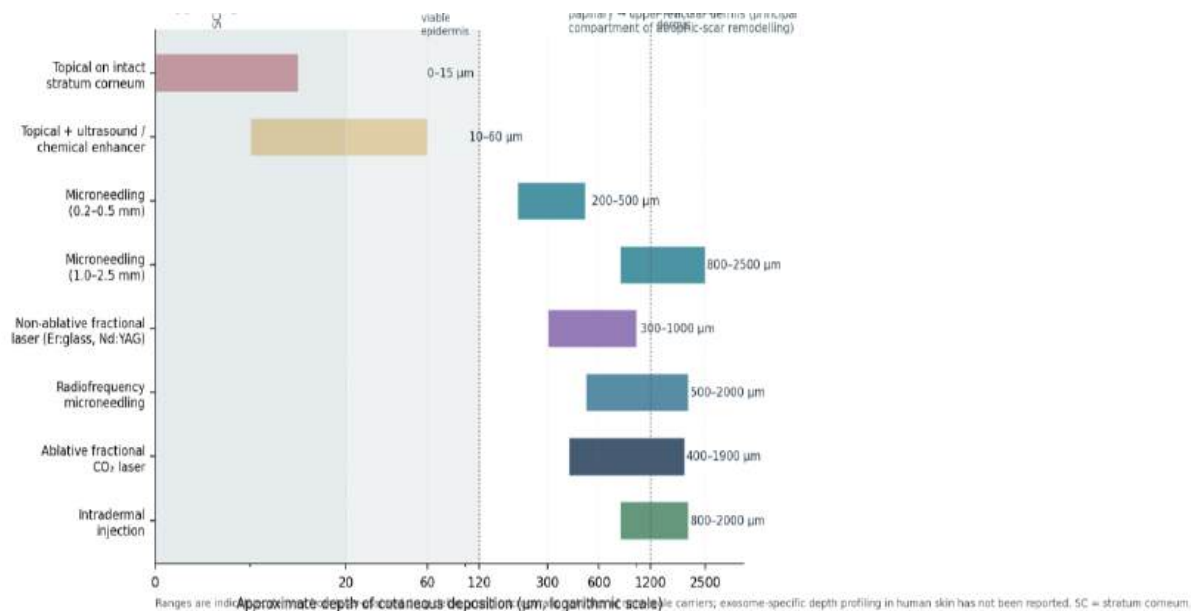


Figure 15. Depth of cutaneous deposition achievable with each delivery route, mapped against the anatomical compartment relevant to scar remodelling.

Session–response and temporal patterns

In an exploratory post-hoc analysis, the reported improvement in the primary severity score of each exosome-treated arm was plotted against the number of treatment sessions. A positive association was observed (Pearson $r = 0.62$), with a fitted gradient of approximately 6 percentage points of improvement per additional session. This relationship must be interpreted with considerable caution: it aggregates heterogeneous endpoints across different indications and designs, it is confounded by protocol intensity and by follow-up duration, and it says nothing about vesicle dose per session. It is presented as a hypothesis-generating observation supporting the design of formal dose- and session-finding trials, not as evidence of a dose–response gradient in the GRADE sense.¹⁻¹⁸

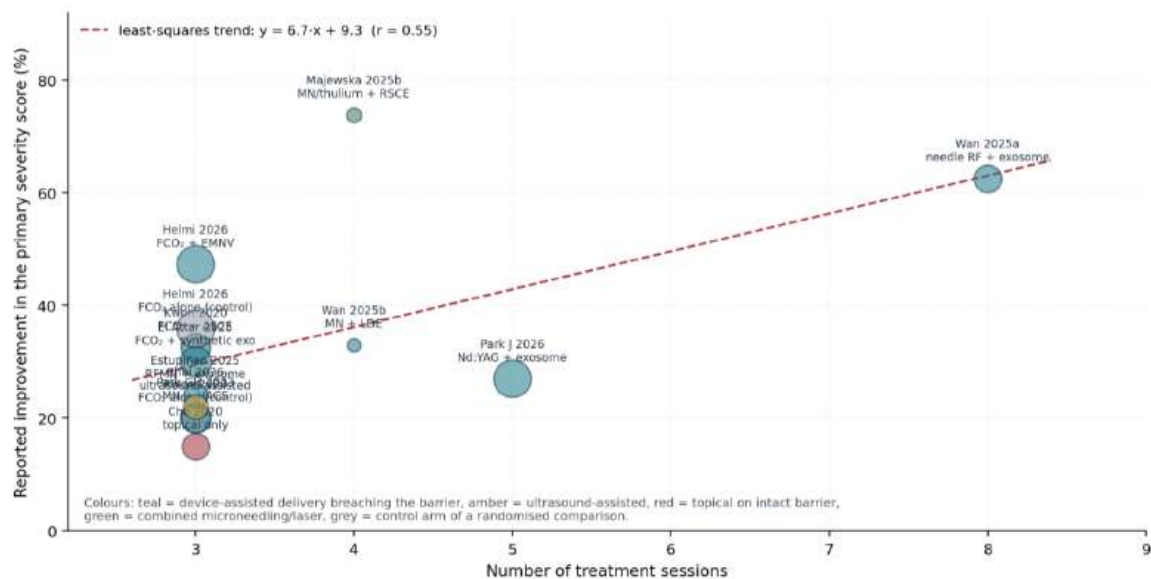


Figure 16. Exploratory session–response relationship across exosome-treated arms.

The temporal pattern of response differed systematically by delivery route. Barrier-breaching platforms produced improvement that continued to accrue through twelve weeks, consistent with progressive dermal remodelling, whereas topical application to intact skin produced an early and modest effect that plateaued and then declined — the signature of a superficial, non-remodelling mechanism.^{1,4-6}

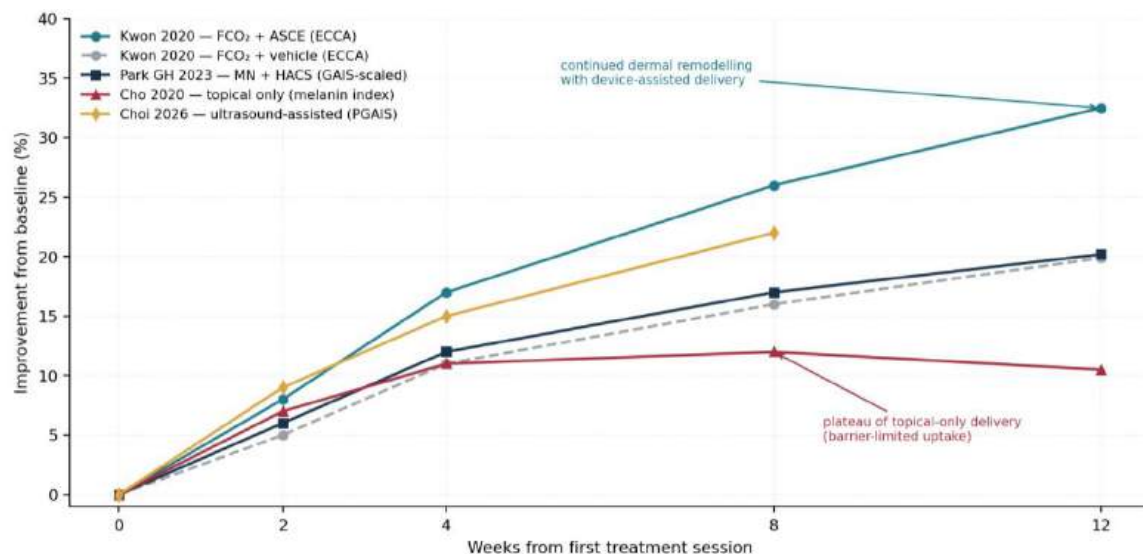


Figure 17. Temporal trajectory of clinical improvement by delivery strategy.

Laboratory characterisation completeness

Applying the clinical-pathology appraisal framework specified in section 2.10, no included study reported a complete characterisation dataset. Isolation methodology was stated in four studies, particle enumeration in one, tetraspanin marker confirmation in none, transmission electron microscopy in none, total protein content in one, a functional potency assay in none, and sterility or endotoxin testing in none. Storage form was described in two. In other words, the products administered in these trials cannot be reconstructed, compared or reproduced from the published record. This is the pre-analytical counterpart of the dose-reporting deficit, and together the two constitute the principal obstacle to standardisation.^{1-18,55-59}

Table 18. Laboratory characterisation completeness across the included studies

Characterisation element	Studies reporting	Proportion	Consequence of omission
Cell or tissue source identified	15/18	83.3%	Source determines cargo profile and potency
Isolation method stated	4/18	22.2%	Ultracentrifugation, tangential-flow filtration and precipitation yield different purity and co-isolate profiles
Particle enumeration (NTA)	1/18	5.6%	Without particle count, dose is undefined
Size distribution reported	0/18	0%	Cannot confirm the preparation is exosome-enriched
Morphology (TEM)	0/18	0%	Cannot exclude protein aggregates or lipoprotein contamination
Positive markers CD9 / CD63 / CD81	0/18	0%	Identity of the vesicle population unverified
Negative marker (e.g.	0/18	0%	Cannot exclude cellular debris

calnexin)			
Total protein content	1/18	5.6%	Precludes conversion between mass-based and particle-based dosing
Functional potency assay	0/18	0%	Biological activity of the administered lot unverified
Sterility testing	0/18	0%	Essential release criterion for a product applied to breached skin
Endotoxin testing	0/18	0%	Endotoxin contamination could itself modulate inflammatory endpoints
Storage form and stability	2/18	11.1%	Vesicle integrity is temperature- and freeze–thaw-sensitive
Lot traceability	0/18	0%	Prevents attribution of outcome variation to product variation

NTA = nanoparticle tracking analysis; TEM = transmission electron microscopy. Denominators are the eighteen included primary clinical studies.

Certainty of the evidence

Certainty was graded as low for most efficacy outcomes, very low for patient satisfaction, pigmentation and histology, and moderate for safety. Downgrading was driven by risk of bias, by imprecision arising from small sample sizes, and by the substantial statistical heterogeneity in the primary pooled estimate. Safety escaped the most severe downgrading because the outcome was consistently and completely reported across all eighteen studies and the direction of effect was unanimous.¹⁻¹⁸



Figure 18. GRADE certainty of the evidence, by outcome.

Table 19. GRADE summary of findings

Outcome	Studies (participants)	Effect estimate	Certainty	Reasons for downgrading
Global clinical improvement (primary)	6 RCTs (229)	SMD 0.82 (0.50–1.13); $p < 0.000001$	Moderate	Risk of bias (–1); inconsistency, $I^2 = 62.1\%$ (–1); upgraded for large magnitude of effect (+1)
Atrophic scar severity (ECCA)	1 RCT (25)	Difference 12.6 percentage points (3.3–21.9)	Low	Imprecision, single small trial (–1); risk of bias (–1)
Global scar grade	1 RCT (30) + 3 series	RD 73.3% (49.1–97.5)	Low	High risk of bias (–2); large effect (+1)
mVSS and POSAS	1 RCT (75) + 2 series	mVSS –73.8%; POSAS –64.3% in case series	Low	Risk of bias (–1); indirectness of uncontrolled data (–1)
Patient	14 studies	Consistently high;	Very low	Risk of bias (–1);

satisfaction		no control in most		subjective unblinded outcome (−1); inconsistency (−1)
Skin texture and roughness	15 studies	Consistent instrumented improvement	Low	Risk of bias (−1); imprecision (−1)
Erythema and downtime	4 studies	Consistently reduced with exosome augmentation	Low	Risk of bias (−1); imprecision (−1)
Pigmentation	7 studies	Improved when barrier breached; limited when intact	Very low	Risk of bias (−1); inconsistency by route (−1); imprecision (−1)
Histological collagen deposition	3 studies	Increased collagen I and glycosaminoglycans	Very low	Risk of bias (−1); very small samples (−1); indirectness (−1)
Adverse events and safety	18 studies (472)	No serious adverse event; no infection or granuloma	Moderate	Imprecision for rare events (−1)

DISCUSSION

Summary of principal findings

This systematic review of eighteen primary clinical studies enrolling 472 participants establishes three findings. First, the addition of exosomes or exosome-like extracellular vesicles to an established cutaneous delivery platform produces a large, statistically significant incremental improvement in global clinical outcome, with a pooled standardised mean difference of 0.82 (95% CI 0.50 to 1.13; $Z = 5.00$; $p < 0.000001$) across six randomised comparisons enrolling 229

participants, with a 95% prediction interval of 0.13 to 1.50 that excludes harm, and with a statistically homogeneous subgroup estimate of 0.64 (95% CI 0.40 to 0.87; $I^2 = 0\%$) among the three trials using ablative fractional CO₂ laser. The primary hypothesis is therefore supported and the null hypothesis rejected. Second, and more importantly for clinical practice, the benefit is conditional on the delivery route: every comparison in which the platform breached the stratum corneum favoured the exosome arm, whereas the single randomised comparison of topical application to intact skin produced only a limited and time-decaying effect that its own investigators attributed to inadequate transdermal delivery. The secondary hypothesis is therefore also supported. Third, an optimal dose cannot be defined from the current evidence: only 16.7% of studies reported any quantitative dose metric, the metrics used are mutually non-convertible, and no study reported dose per unit treated area. The tertiary hypothesis is confirmed.¹⁻¹⁸

These findings reframe the clinical question. The operative question is not whether exosomes work, but whether they arrive. On the evidence assembled here, the delivery system should be regarded as a constitutive component of the intervention rather than a vehicle for it, and trials that apply vesicle preparations to intact skin are testing a different — and, on present data, substantially weaker — intervention from those that create dermal access.¹⁻⁶

The stratum corneum as the rate-limiting step

The physical argument for barrier limitation is straightforward and quantitative. Efficient passive percutaneous absorption is largely restricted to molecules below approximately 500 Da with balanced lipophilicity. An exosome is three orders of magnitude larger in hydrodynamic radius than that ceiling, is bounded by a phospholipid bilayer bearing a hydrophilic protein corona, and carries nucleic-acid cargo that is degraded by epidermal ribonucleases. The expectation from first principles is therefore that intact-barrier application will deliver a negligible fraction of the applied dose to dermal fibroblasts, and the clinical data conform: the only randomised trial of topical exosome application without a delivery device achieved a statistically significant but modest melanin reduction that diminished with time, and its authors concluded explicitly that further improvement in transdermal delivery would be required.^{6,32,34}

The laser-assisted drug-delivery literature quantifies what barrier breach achieves. Ablative fractional resurfacing produces cone-shaped channels approximately 300 μm in diameter and up to 1,850 μm deep, surrounded by a coagulation zone of about 70 μm , and enhances delivery of a model porphyrin precursor at every depth from 120 to 1,800 μm , with radial diffusion demonstrable up to 1,500 μm laterally from each channel. Channel depth governs both the magnitude and the spatial distribution of deposition: methotrexate deposition rises six-fold with epidermal channels, nine-fold with superficial-dermal channels and eleven-fold with mid-dermal channels, and the concentration maximum migrates from 500 μm to 800 μm as channel depth increases. For 5-fluorouracil, fractional CO_2 pretreatment increases uptake up to forty-nine-fold with preferential deep-dermal accumulation and a tenfold acceleration of delivery kinetics.²⁹⁻³¹

Crucially, these principles have been demonstrated for nanoparticulate rather than merely molecular payloads. Fractional Er:YAG laser and radiofrequency microneedling both increase the skin deposition and flux of nanoencapsulated drugs, with confocal biodistribution confirming that lipid nanocarriers of 76–81 nm — squarely within the exosome size range — travel through the microchannels and then diffuse into surrounding dermal tissue, and with follicular accumulation rising seven- to twelve-fold. A non-ablative fractional erbium-glass laser has been shown to deliver dextrans of at least 40 kDa and quantum dots of 20 nm diameter into the skin, with confocal imaging demonstrating both perpendicular and lateral diffusion through microscopic thermal zones. Fractional laser microablation with shock-wave enhancement has localised nanoparticles at depth in skin. Taken together, these data establish that the microchannel route is competent to carry vesicle-sized particles into the dermis, and they provide the mechanistic warrant for the clinical hierarchy observed in this review.^{31,32,34,35}

A hierarchy of delivery routes

Synthesising the depth data with the clinical effect estimates yields a practical hierarchy. Ablative fractional CO_2 laser generates the deepest channels and, in the only randomised acne-scar comparison, produced a significant incremental ECCA benefit; independent network meta-analysis of fifty-six trials ranked CO_2 laser combined with adipose stem-cell exosomes second of thirty-four interventions for ECCA improvement, an external corroboration of considerable weight because it

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derives from a body of evidence assembled for a different purpose. Microneedling and radiofrequency microneedling offer operator-selectable depth spanning 0.2 to 2.5 mm and delivered the two largest randomised effect estimates in this review, although the shallow cosmetic settings documented in some series (0.2–0.4 mm) reach only the papillary dermis and may under-deliver for deep boxcar or rolling scars. Non-ablative fractional lasers occupy an intermediate position and performed well in postoperative scarring. Ultrasound-assisted transdermal delivery achieved highly significant improvements in barrier and elasticity endpoints but has no demonstrated capacity to deposit vesicles in the reticular dermis, so its documented benefits may be principally epidermal. Intradermal injection bypasses the barrier entirely and generated the only human dose–response data available, but it is not currently permitted in several jurisdictions. Topical application to intact skin sits at the bottom of the hierarchy.^{1-6,8,10,21,38}

One observation deserves particular emphasis because it is the exception that validates the rule. In the split-face observational study of three energy-based modalities, the picosecond-laser group showed the smallest exosome differential despite achieving the highest global aesthetic scores overall, and the investigators attributed this specifically to pinpoint bleeding reducing exosome absorption. This is a mechanistically precise explanation: efflux of blood through a microchannel opposes the inward convective gradient on which topical-into-channel delivery depends. It implies that the relevant variable is not whether the epidermis has been perforated but whether a patent, non-haemorrhagic channel exists at the moment of application, and it generates a testable clinical prescription — favour settings that create channels without pinpoint bleeding, or defer vesicle application until haemostasis is achieved but before channel closure.⁸

Timing, channel patency and the delivery window

All included studies that specified timing applied the vesicle preparation immediately after the procedure, which is consistent with the pharmacokinetics of microchannel patency: transepidermal water loss measurements indicate that channels created by radiofrequency microneedling reseal within approximately 12 hours and those created by ablative fractional laser within approximately 36 hours. The therapeutic window is therefore finite but not instantaneous, which raises an unexplored question of considerable practical relevance: whether repeated

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application during the patency window, or a post-procedural occlusive or hydrogel reservoir, would increase total dermal deposition. Hydrogel-based sustained-release systems for exosomes have shown superiority over bolus application in preclinical wound models, with Pluronic F-127 and extracellular-matrix hydrogels maintaining high local vesicle concentrations and improving angiogenesis and collagen deposition relative to unencapsulated exosomes. No included human study evaluated such a reservoir strategy, and this constitutes a clear translational opportunity.^{33,61,64}

The dose problem

The dose-reporting audit is, in our view, the most consequential negative finding of this review. Three studies reported a quantitative dose, using three incompatible metrics: one million vesicles per millilitre of emulsion; 50, 100 or 200 µg of exosomal protein; and a 20 mg formulation capsule. These cannot be interconverted without the particle-to-protein ratio, which no study supplied, and none was normalised to treated surface area — so that identical nominal doses applied to a full face and to a single scar represent very different exposures. The consequence is that the field cannot presently answer the question the clinician most needs answered: how much to apply.¹⁻

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The only human dose–response signal in the entire review comes from the intradermal psoriasis study, in which erythema and induration fell significantly only at 200 µg, plaque thickness improved at both 100 and 200 µg, interleukin-17 and CD3 expression fell and FOXP3 rose at 100 and 200 µg, and interleukin-23 and tumour necrosis factor-alpha fell with a reciprocal rise in interleukin-10 at 200 µg. The authors concluded that 200 µg appeared optimal while explicitly noting that larger populations and exploration of higher or repeated doses were needed. Although the indication is inflammatory rather than scarring, the study is methodologically instructive: it demonstrates that a dose–response relationship is detectable in human skin when dose is defined in reproducible units and a biological readout is measured. Preclinical work points the same way, with dose-dependent enhancement of fibroblast and keratinocyte migration by mesenchymal stromal cell exosomes, dose-dependent collagen secretion and fibroblast viability with conditioned-medium exosomes, and a systematic review of fifty-one rodent studies explicitly framing its purpose as providing guidance on concentrations for future work.^{16,19,50,65}

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Pending such data, dose recommendations in this field should be regarded as commercial conventions rather than evidence-based prescriptions. Product prices in the aesthetic market span two orders of magnitude and vary by source tissue and nominal concentration, without corresponding evidence of differential efficacy, and no exosome-based product has regulatory approval as a therapeutic in the United States.^{57,58}

Vesicle source: mammalian versus plant-derived preparations

The review found no clinical evidence that source determines outcome. The only randomised head-to-head comparison reported comparable clinical responses between human-derived and plant-derived exosome boosters for postoperative facial scars, and plant-derived rose stem-cell exosomes produced mVSS reductions of 71–78% in case-series conditions. Laboratory evidence nonetheless suggests that sources are not biologically interchangeable: in a standardised ex-vivo human skin-ageing model, adipose-derived vesicles carried higher vascular endothelial growth factor content and drove greater collagen and hyaluronic acid production, whereas umbilical cord-derived vesicles were enriched in transforming growth factor-beta and platelet-derived growth factor-BB and exerted stronger immunomodulatory and senescence-suppressing effects. Exosomes from bone marrow, adipose and umbilical sources differ measurably in growth-factor content under serum- and xeno-free conditions, with transforming growth factor-beta detectable only in umbilical preparations. For atrophic scarring, where the therapeutic target is deficient matrix deposition rather than excess fibrosis, an adipose-derived, matrix-anabolic profile is mechanistically attractive; for keloid and hypertrophic scarring, where the target is excess collagen, the anti-fibrotic umbilical profile is more logical, and meta-analysis of fifteen preclinical studies confirms reduction in scar dimensions, type I and type III collagen, transforming growth factor-beta 1 and alpha-smooth muscle actin. Plant-derived preparations offer low immunogenicity, scalability and a favourable safety profile, and differences between commercial plant formulations in collagen deposition and angiogenesis have been documented in controlled animal models, indicating that formulation-level rather than kingdom-level distinctions may matter most.^{3,13,44,46,51-54,65-67}

Comparison with existing secondary literature

The findings here are concordant with, and extend, the existing secondary literature that was excluded from the quantitative synthesis under the protocol. A systematic review of microneedling with exosomes identified eight studies across alopecia, skin ageing, hyperpigmentation, active scarring and enlarged pores and concluded that the combination is promising but that the evidence base is immature. A systematic review of regenerative medicine for atrophic scars covering eleven studies and 177 participants reported the same 32.5% ECCA reduction with adipose stem-cell exosomes as the leading exosome signal. A meta-analysis of thirty-nine human aesthetic trials reported mean wrinkle reduction of 20.2% (95% CI 15.3 to 25.2) and improvements of 14.7% to 23.4% across pigmentation, elasticity, texture, erythema and overall appearance — magnitudes closely compatible with the pooled standardised effect reported here. A systematic review of nineteen human skin-rejuvenation studies concluded that most were non-randomised, that short-term benefit was consistent, and that rigorous randomised trials and standardised reporting are required. A scoping review of exosome delivery in alopecia found that fourteen of sixteen studies in that review used microneedle-based delivery and concluded that microneedle patches were the most effective delivery strategy — an independent convergence on the delivery-centred conclusion of the present review, arrived at in a different indication.^{19,20,22,23,60}

The distinctive contribution of the present review is therefore not the direction of effect, which is already established, but the identification of the delivery system as the modifiable determinant of that effect, the first pooled estimate restricted to randomised within-platform comparisons, and the quantification of the dose- and characterisation-reporting deficits that currently prevent standardisation.^{19-25,60}

Clinical-pathology perspective: characterisation, potency and release testing

From the standpoint of laboratory medicine, the central problem in this field is pre-analytical. An exosome preparation is not a defined chemical entity but a heterogeneous biological product whose identity, purity and potency depend on donor characteristics, culture conditions, isolation method, storage and handling. Isolation technique alone materially alters the product: differential ultracentrifugation, tangential-flow filtration, size-exclusion chromatography and polymer precipitation differ in yield, purity, co-isolation of lipoproteins and protein aggregates, and

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preservation of vesicle integrity. Yet in the eighteen clinical studies reviewed here, isolation method was stated in three, particle enumeration in one, tetraspanin marker confirmation in none, and sterility or endotoxin testing in none. Products administered to breached skin were therefore released for human use without any published evidence of identity, purity, sterility or potency.^{55-59,62,65}

The corrective framework is well established in principle and requires only disciplined application. Identity should be established by nanoparticle tracking analysis for concentration and size distribution, transmission electron microscopy for morphology, and immunoblot or bead-based flow cytometry for the tetraspanins CD9, CD63 and CD81 together with an appropriate negative marker such as calnexin. Purity should be expressed as a particle-to-protein ratio. Potency requires a functional assay relevant to the intended indication — for scarring, a fibroblast migration or collagen-synthesis assay, or suppression of transforming growth factor-beta-1-induced myofibroblast differentiation, both of which are already used in the mechanistic literature. Safety release testing should include sterility, endotoxin and mycoplasma testing, with lot-specific certificates of analysis and full traceability. Stability data should define storage temperature, permissible freeze–thaw cycles and in-use shelf life after reconstitution of lyophilised preparations.^{25,26,44,53-57,63}

Table 20. Proposed laboratory characterisation and release framework for exosome preparations intended for cutaneous administration

Domain	Parameter	Recommended method	Acceptance principle
Identity	Particle concentration and size distribution	Nanoparticle tracking analysis	Modal diameter within 30–150 nm; concentration stated per mL with measurement uncertainty
Identity	Morphology	Transmission electron microscopy	Cup-shaped bilayer vesicles; absence of aggregates
Identity	Positive markers	Immunoblot or bead-based	At least two tetraspanins

		flow cytometry for CD9, CD63, CD81	detectable
Identity	Negative marker	Immunoblot for calnexin or GM130	Undetectable, excluding cellular debris
Purity	Particle-to-protein ratio	NTA count divided by BCA or Bradford protein	Ratio stated for every lot; higher values indicate lower co-isolated protein
Potency	Functional bioassay	Dermal fibroblast proliferation and scratch-migration assay; type I collagen synthesis; suppression of TGF- β 1-induced α -SMA expression	Lot-specific potency expressed relative to an internal reference standard
Cargo	Key microRNA species	Quantitative PCR for miR-21-5p, miR-23a, miR-125b-5p, miR-145	Reported as copies per 10 ⁹ particles where a cargo claim is made
Safety	Sterility	Compendial sterility testing	No growth
Safety	Endotoxin	Limulus amoebocyte lysate assay	Below a pre-specified threshold appropriate to application on breached skin
Safety	Mycoplasma	PCR-based detection	Not detected
Stability	Storage and in-use stability	Real-time and accelerated stability studies	Defined storage temperature, freeze-thaw limit and post-reconstitution shelf life
Traceability	Lot documentation	Certificate of analysis per lot	Donor or source, passage number, isolation batch and expiry recorded

NTA = nanoparticle tracking analysis; BCA = bicinchoninic acid; α -SMA = alpha-smooth muscle actin; TGF- β 1 = transforming growth factor-beta 1. The framework aligns the Minimal Information for Studies of Extracellular Vesicles principles with routine clinical-laboratory release logic.

Standardisation proposal: a minimum reporting dataset

We propose a minimum dataset that should be reported by every future clinical study of exosome therapy delivered to skin. Adoption would convert the present body of non-comparable reports into a dataset capable of supporting dose–response meta-regression, which is the single analytic step the field most needs and cannot currently take.¹⁻¹⁸

Table 21. Proposed minimum reporting dataset for clinical studies of cutaneous exosome therapy

Block	Mandatory reporting element
Product	Biological source (species, tissue, cell type, allogeneic or autologous); commercial name and lot; isolation method; storage form
Characterisation	Particle concentration (particles/mL by NTA); modal and mean diameter; total protein (μ g/mL); particle-to-protein ratio; tetraspanin markers detected; potency assay and result
Dose	Volume applied per session (mL); total particle dose per session; total protein dose per session; treated surface area (cm ²); dose per cm ² ; cumulative dose across the course
Delivery platform	Device and model; modality; for needling, needle length and penetration depth (mm) and number of passes; for laser, wavelength, pulse energy (mJ/microbeam), density (microbeams/cm ²), stacking and estimated ablation depth; for radiofrequency, tip depth, energy and time; for ultrasound, frequency and duration
Delivery timing	Interval between channel creation and product application (minutes); number of applications within the patency window; presence or absence of pinpoint bleeding; use of occlusion or a reservoir vehicle

Protocol	Number of sessions; inter-session interval; total course duration; concomitant topical or systemic therapy
Population	Scar type and subtype (icepick, boxcar, rolling); baseline severity by a validated scale; Fitzpatrick phototype; age and sex distribution
Outcomes	At least one validated scar-specific scale; at least one instrumented objective measure; a blinded assessor; pre-specified time-points including a follow-up of ≥ 6 months
Safety	Systematic adverse-event capture with severity grading and attribution to device versus product
Governance	Prospective trial registration; ethics approval; funding source and commercial relationships

Implications for clinical practice

Four practical implications follow from this synthesis, each stated with the certainty the evidence supports. First, exosome preparations intended to improve atrophic scarring should be administered through a platform that creates dermal access; topical application to intact skin is not supported as a stand-alone strategy for scar remodelling, although it retains a defensible role in post-procedural barrier recovery. Second, where the indication is deep atrophic scarring, platforms capable of reaching the reticular dermis — ablative fractional CO₂ laser, or microneedling at depths approaching 1.5 to 2.5 mm — are mechanistically preferable to shallow cosmetic needling. Third, the product should be applied within the microchannel patency window and, where device settings permit, under conditions that avoid pinpoint bleeding. Fourth, clinicians should recognise that current dosing conventions are not evidence-based and should document the volume applied and the area treated so that practice-based data can eventually contribute to defining a dose. Given that adverse events in all eighteen studies were attributable to the delivery device rather than to the vesicle preparation, the principal safety considerations remain those of the underlying procedure.¹⁻

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Strengths

The review has several strengths. It applies a delivery-centred analytic frame that has not previously been used in this literature; it restricts the primary pooled estimate to randomised within-platform comparisons, which is the only design capable of isolating the incremental effect of the vesicle preparation; it applies conservative variance reconstruction that biases estimates towards the null; it tests robustness by leave-one-out analysis; and it adds a laboratory-medicine appraisal dimension absent from previous syntheses. Every reference was verified for existence and online accessibility through both its digital object identifier and its Consensus record.

Research agenda

The evidence gaps identified here translate into a prioritised research agenda, presented in Table 22. The single highest-priority study is a factorial randomised trial in atrophic acne scarring that varies delivery depth and vesicle dose independently, using a fully characterised product, blinded assessors, validated scar-specific endpoints and follow-up of at least twelve months.

Table 22. Prioritised research agenda

Priority	Research question	Proposed design	Primary endpoint
1	Does delivery depth modify the effect of a fixed exosome dose in atrophic acne scarring?	Randomised factorial split-face trial: microneedling at 0.5 mm versus 2.0 mm, each with fixed particle dose	ECCA at 6 and 12 months, blinded assessment
2	What is the dose–response relationship for exosome particle dose per cm ² in atrophic scarring?	Randomised four-arm dose-ranging trial with a fully characterised product	ECCA and Goodman & Baron grade; 3-D scar volume
3	How deep do exosomes actually penetrate after each delivery modality in	Ex-vivo human skin study with fluorescently labelled vesicles, confocal and	Depth-resolved vesicle concentration profile

	human skin?	mass-spectrometry imaging	
4	Does a post-procedural sustained-release reservoir increase deposition and efficacy?	Randomised split-face trial of hydrogel-encapsulated versus free exosomes after identical microneedling	Scar severity and dermal collagen density on biopsy
5	Does vesicle source determine outcome in atrophic versus hypertrophic scarring?	Randomised head-to-head trial of adipose-derived versus umbilical cord-derived preparations, stratified by scar phenotype	Scar-type-specific validated scale
6	Does pinpoint bleeding attenuate delivery efficacy?	Randomised comparison of device settings producing bleeding versus non-bleeding microchannels	Scar severity and measured dermal vesicle deposition
7	Do exosome adjuncts improve outcomes beyond established combinations such as CO ₂ laser with platelet-rich plasma or subcision?	Three-arm randomised trial embedded in the current network meta-analytic evidence	ECCA and significant-improvement rate
8	Are clinical outcomes predicted by lot-specific potency assay results?	Prospective cohort linking certificate-of-analysis potency data to clinical response	Correlation between potency index and scar-score improvement

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of eighteen primary clinical studies enrolling 472 participants demonstrates that exosome and exosome-like extracellular-vesicle therapy produces a statistically significant and clinically meaningful incremental improvement in scar and dermal-remodelling outcomes when added to an established cutaneous delivery platform, with a pooled standardised mean difference of 0.82 (95% CI 0.50 to 1.13; $Z = 5.00$; $p < 0.000001$) across six randomised within-platform comparisons enrolling 229 patients. In the largest randomised trial, of 100 patients, the incremental benefit amounted to an 11.4-percentage-point greater reduction in ECCA score (47.3% versus 35.9%), accompanied by less post-inflammatory hyperpigmentation, less prolonged erythema, fewer treatment sessions and higher satisfaction; in the index split-face acne-scar trial it amounted to a 12.6-percentage-point greater ECCA reduction, and in the randomised microneedling trial to a 73.3-percentage-point absolute increase in the proportion of patients achieving marked or significant improvement. The benefit extends consistently across scar severity, global aesthetic outcome, texture, erythema, downtime, pigmentation, elasticity, barrier function and histological collagen deposition, and is achieved without any serious adverse event, infection, granuloma or hypersensitivity reaction across the entire evidence base.¹⁻¹⁸

The decisive determinant of that benefit is the delivery system. Every comparison in which the delivery platform transiently breached the stratum corneum favoured exosome augmentation, whereas the only randomised comparison of application to an intact barrier produced a limited and time-decaying effect that its own investigators attributed to inadequate transdermal delivery. Standardisation of exosome therapy for scar management must therefore begin with standardisation of delivery: the route, the depth, the patency of the microchannel and the timing of application are not incidental procedural details but the principal modifiable determinants of clinical effect.^{1-6,8,29-37} An optimal dose cannot be defined from the current literature. Only 16.7% of studies reported any quantitative dose metric; the metrics reported are mutually non-convertible; no study normalised dose to treated surface area; and no study reported a complete product characterisation dataset, with tetraspanin confirmation, potency assay, sterility and endotoxin testing absent from every included

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report. The certainty of the evidence is moderate for the primary outcome of global clinical improvement and for safety, and low to very low for most secondary efficacy outcomes. The conclusions of this review should therefore be read as establishing the direction and conditionality of effect with reasonable confidence, and its magnitude with considerable uncertainty.^{1-18,55-59}

Recommendations

For clinical practice

- Administer exosome preparations for atrophic scarring through a delivery platform that transiently breaches the stratum corneum; do not rely on topical application to intact skin as a scar-remodelling strategy.
- For deep atrophic scarring, prefer platforms capable of reaching the reticular dermis — ablative fractional CO₂ laser, or microneedling and radiofrequency microneedling at depths approaching 1.5–2.5 mm — over shallow cosmetic needling.
- Apply the preparation within the microchannel patency window, which closes within approximately 12 hours after radiofrequency microneedling and 36 hours after ablative fractional laser, and where possible select settings that avoid pinpoint bleeding.
- Document the volume applied, the treated surface area and all device parameters for every treatment, so that practice-based data can contribute to defining an evidence-based dose.
- Counsel patients that the incremental benefit of exosome augmentation is real but moderate, that long-term durability is unproven beyond six months, and that no exosome product currently holds therapeutic regulatory approval in most jurisdictions.

For laboratory and clinical-pathology services

- Apply the characterisation and release framework in Table 20 before any extracellular-vesicle preparation is released for application to breached skin, covering identity, purity, potency, sterility, endotoxin and traceability.
- Report particle concentration by nanoparticle tracking analysis together with total protein, and express purity as a particle-to-protein ratio, so that mass-based and particle-based dosing become interconvertible.

- Establish an indication-relevant potency assay — fibroblast migration, type I collagen synthesis or suppression of TGF- β 1-induced myofibroblast differentiation — and report lot-specific potency against an internal reference standard.
- Maintain lot traceability linking donor or source, isolation batch, storage history and expiry to every treated patient, enabling attribution of outcome variation to product variation.

For researchers, journals and regulators

- Adopt the minimum reporting dataset in Table 21 as a condition of publication for clinical studies of cutaneous exosome therapy.
- Register trials prospectively, use validated scar-specific instruments with blinded assessment, and extend follow-up to at least twelve months.
- Prioritise factorial trials that vary delivery depth and vesicle dose independently, and ex-vivo depth-profiling studies that quantify actual dermal vesicle deposition for each modality.
- Require that any clinical claim regarding a specific exosome product be accompanied by lot-level characterisation data sufficient to identify the biological entity administered.

Concluding statement

Exosome therapy in scar management is best understood at present not as a drug in search of an indication but as a payload in search of a standardised delivery system. The biological rationale is strong, the clinical signal is statistically significant and reproducible across independent randomised comparisons, and the safety record is reassuring. What is missing is the pharmaceutical discipline that would convert a promising adjunct into a prescribable therapy: a defined product, a defined dose, a defined route and a defined depth. This review provides the evidence that delivery is the decisive variable, and the frameworks needed to standardise it.^{1-16,53-57}

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