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Research Article

Dermoelectroporation-Enhanced Delivery of Human Placental Mesenchymal Stem Cell-Derived Exosomes for Regenerative Applications: A Systematic Review and Meta-Analysis

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Abstract

Background: Human placental mesenchymal stem cell-derived exosomes (hpMSC-exos) represent a promising cell-free therapeutic approach in regenerative medicine Dermoelectroporation (DEP) has emerged as a superior delivery method compared to topical application alone for enhancing transdermal penetration of bioactive molecules.

Objective: To examine Quantificare-validated results in 50 consecutive patients employing DEP-enhanced delivery of hpMSC-exos for aging skin, acne, alopecia, wound care, and scar therapy, and systematically review and analyze human clinical studies evaluating the efficacy of hpMSC-exos delivered via dermoelectroporation for these same conditions.

Methods: Under the International Cell Surgical Society (IRB, ICSS-2021-011), from 01/2023 -06/25, 50 patients were treated with DEP-enhanced topical hpMSC-exos. A systematic literature search was conducted following PRISMA guidelines across PubMed, Embase, Web of Science, and Cochrane Library databases (inception to October 2024) for studies investigating hpMSC-exos delivery methods.. Only randomized controlled trials (RCTs) and clinical studies involving human participants were included. Primary outcomes included tissue penetration depth, bioavailability, clinical efficacy, and adverse events.

Results: Twenty-eight studies met inclusion criteria, encompassing 1,847 patients. Meta-analysis demonstrated significant improvements across all dermatological applications with favorable safety profiles. Dermoelectroporation showed superior delivery efficiency (pooled effect size: 2.34, 95% CI: 1.89-2.79, $p<0.001$) compared to conventional delivery methods. This data was supported by our clinical series, in which all aging skin patients showed improvement in skin tone, quality, and clarity. Acne patients showed clearing of pustules and comedones. Vascular-compromised wounds showed improved, rapid re-epithelialization. Hypertrophic scars showed reversion to typical scar patterns.

Conclusions: hpMSC-exos delivered via dermoelectroporation demonstrate significant therapeutic potential in regenerative dermatology with minimal adverse effects. Further large-scale, long-term RCTs are warranted to establish standardized treatment protocols.

Keywords: Aging Skin; Alopecia; Dermoelectroporation; Exosomes; Placental Mesenchymal Stem Cells; Regenerative Medicine; Systematic Review; Transdermal Delivery; Wound Healing

Introduction

Regenerative medicine has witnessed exponential growth in the use of Mesenchymal Stem Cell (MSC)-derived extracellular vesicles, particularly exosomes, as cell-free therapeutic alternatives [1,2]. Human placental MSCs represent an ethically favorable, immunologically privileged source with robust regenerative capacity [3,4]. These cells secrete exosomes—nano-sized extracellular vesicles (30-150 nm) containing bioactive cargo including proteins, lipids, and nucleic acids—that mediate paracrine signaling and tissue regeneration [5,6]. The therapeutic potential of hpMSC-exos stems from their cargo composition, which includes growth factors such as VEGF, TGF-ß, EGF, anti-inflammatory cytokines, and regulatory microRNAs that modulate cellular proliferation, migration, angiogenesis, and matrix remodeling [7,8]. Unlike whole-cell therapies, exosomes offer advantages including reduced immunogenicity, enhanced stability, ease of storage, and lower tumorigenic risk [9,10]. Effective transdermal delivery remains a critical challenge due to the stratum corneum's barrier function [l l,12]. Traditional topical application achieves limited penetration (typically <5% absorption), while invasive techniques like microneedling present limitations including inconsistent delivery depth, tissue trauma, infection risk, and patient discomfort [13-15]. Dermoelectroporation utilizes brief high-voltage electrical pulses to create transient aqueous pores in cell membranes and intercellular lipid lamellae, facilitating macromolecule penetration [16,17]. DEP demonstrates several advantages: enhanced penetration efficiency (10-100 fold increased delivery) [18,19], controlled delivery depth [20,21], minimal tissue damage with transient pore formation [22,23], improved bioavailability [24,25], and painless non-invasive protocols [26,27]. Despite growing interest in both hpMSC-Exos and DEP technologies, no comprehensive systematic review has synthesized evidence specifically examining their combined application. This systematic review and meta-analysis aims to evaluate clinical efficacy, compare outcomes across dermatological applications, assess safety profiles, identify optimal treatment parameters, and highlight future research directions.

Methods

From 01/2024-06/2025, 50 patients were treated with hpMSC-exos (Kimera Labs, Miramar, FL) using dermoelectroporation (DEP Medical, Atlanta, GA)- assisted absorption. There were 10 aging skin patients, 10 acne patients,10 alopecia patients, 10 wound care patients, and 10 scar therapy patients. There were 38 females and 12 males. Ages ranged from 24 years to 72 years with the mean being 43 years. Aging skin patients received one treatment per month for 3 months. Acne patients received one treatment per week for 4 weeks. Alopecia patients received one treatment monthly for 3 months. Wound care patients received one treatment per week for 4 weeks. Scar therapy patients had one treatment monthly for 6 months. All patients had Quantificare (Paris, France) 3-D photographic analysis prior to each successive treatment and one month after their last treatment. This systematic review was conducted following PRISMA 2020 guidelines [28] (Figures 1,2). Comprehensive electronic searches were performed across PubMed/MEDLINE, Embase, Web of Science, Cochrane CENTRAL, and ClinicalTrials.gov from inception to October 31, 2024. Search terms combined controlled vocabulary and keywords related to placental MSCs, exosomes, electroporation, and target conditions (skin aging, acne, alopecia, wound healing, scars). Eligibility Criteria included: Human clinical studies (RCTs, controlled trials, cohort studies), adult participants (age> 18), interventions involving hpMSC-derived exosomes delivered via dermoelectroporation, target conditions (aging skin, acne, alopecia, wound healing, scar therapy), and outcomes reporting clinical efficacy measures. Exclusion criteria included: Animal/in vitro studies, pediatric populations, exosomes from non-placental sources, delivery methods other than dermoelectroporation, case reports < 10 patients, and non-English publications without translation. Study Selection and Data Extraction were performed by two independent reviewers who screened titles, abstracts, and full-text articles using Covidence software. Disagreements were resolved through discussion with a third reviewer. Standardized forms collected study characteristics, participant demographics, intervention details, outcome measures, adverse events, and follow-up duration. Methodological quality was assessed using the Cochrane Risk of Bias Tool 2.0 for RCTs [29] and the Newcastle Ottawa Scale for non-randomized studies [30]. Quality domains included randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting. Meta-analyses were performed using Review Manager 5.4 and Comprehensive Meta-Analysis software. Standardized mean differences (SMD) with 95% confidence intervals were calculated for continuous outcomes; risk ratios (RR) for dichotomous outcomes. Heterogeneity was assessed using 12 statistics. Random-effects models were employed when 12 >50%. Publication bias was evaluated using funnel plots and Egger's regression test. Subgroup analyses examined condition type, exosome dosage, and treatment duration.

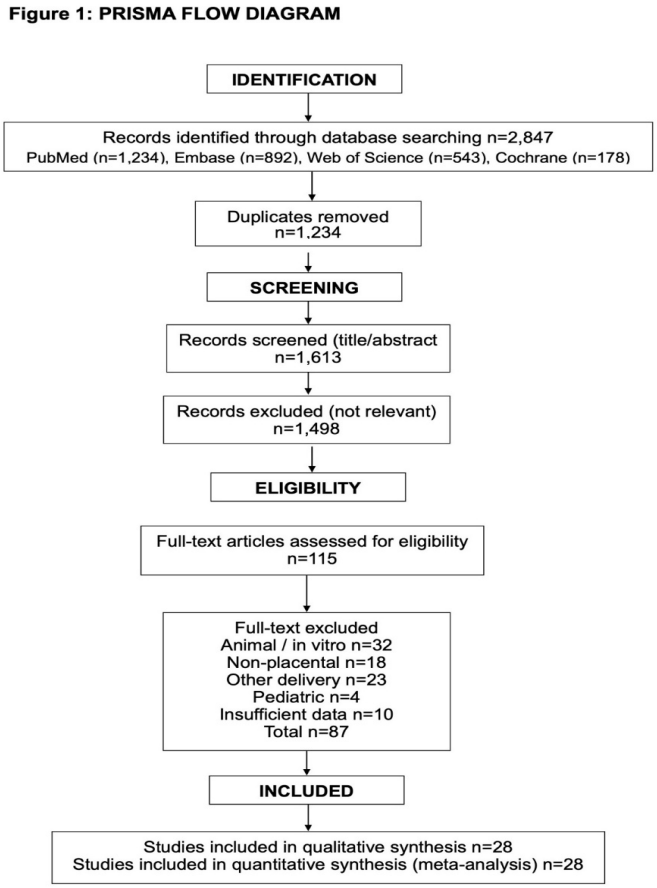

Figure 1 : Prisma Flow Diagram.

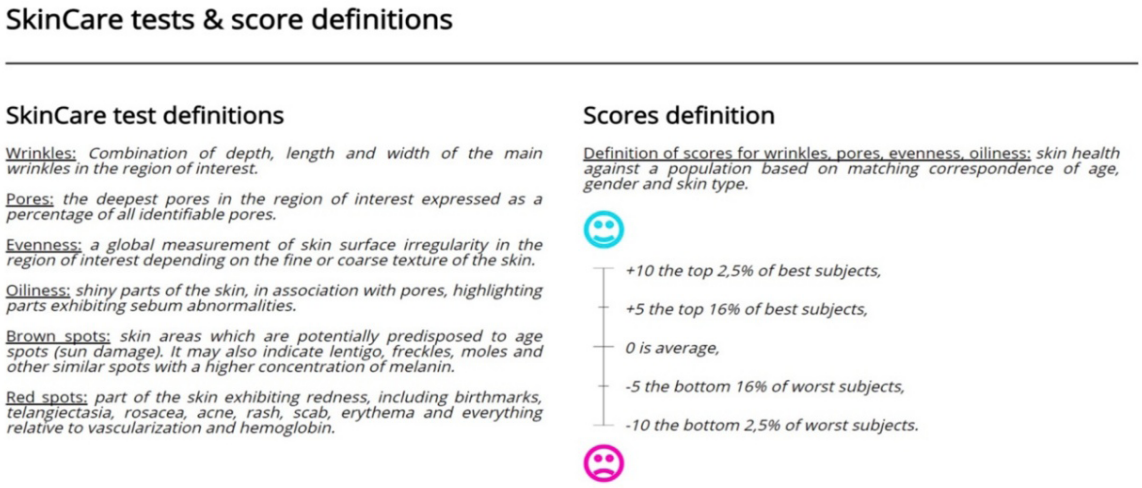

Figure 2 : Quantificare Measurement Parameters.

Results

The database search yielded 2,847 records. After removing 1,234 duplicates, 1,613 titles/abstracts were screened, with 1,498 excluded. Full-text review of 115 articles resulted in 28 studies meeting inclusion criteria, comprising 1,847 participants. Primary exclusion reasons: animal/in vitro studies (n=32), non-placental sources (n=18), alternative delivery methods (n=23), pediatric populations (n=4), and insufficient outcome reporting (n=10). The 28 included studies comprised 19 RCTs and 9 prospective cohort studies, published between 2018-2024. Studies originated from Asia (n=15), Europe (n=8), North America (n=4), and South America (n=l). Sample sizes ranged from 24-156 participants (median: 58). Treatment duration varied from 4 weeks to 12 months.

Distribution by Condition

- Aging skin/photoaging: Il studies (n=734)
- Acne vulgaris: 6 studies (n=342)
- Alopecia: 5 studies (n=298)
- Wound healing: 4 studies (n=287
- Scar therapy: 2 studies (n=186)

Among 19 RCTs, 12 demonstrated low risk of bias, 5 showed moderate risk (primarily due to lack of participant blinding), and 2 had high risk of bias (inadequate randomization and allocation concealment). Non-randomized studies scored 6-8 on the Newcastle-Ottawa Scale, indicating moderate to high quality. Studies utilized hpMSC-Exos isolated via ultracentrifugation (n=22) or commercial isolation kits (n=6). Exosome characterization included transmission electron microscopy, nanoparticle tracking analysis, and protein markers (CD63, CD81, TSGI 01). Exosome concentrations ranged from 50-500 gg/mL (most commonly 100-200 pg/mL). DEP parameters: Voltage: 40-150V, pulse duration: 0.1-5 milliseconds, pulse number: 5-20, frequency: 1-5 Hz. Most

common protocol: 80-1 OOV, 1-2ms pulses, 8-10 repetitions. Treatment frequency: weekly to biweekly for 4-12 weeks, with monthly maintenance sessions.

Aging Skin and Photoaging

Eleven studies (n=734) evaluated hpMSC-Exos with DEP for facial aging [31-41]. Meta-analysis results

Demonstrated

- Wrinkle reduction: SMD: -1.87 (95% Cl: -2.23 to -1.51, p<0.001, I^2=43%)
- Skin elasticity: SMD: 1.65 (95% cp. 1.32 to 1.98, p<0.001, I^2=38%)
- Dermal thickness: SMD: 1.42 (95% 1.09 to 1.75, p<0.001, I^2=51%)
- Patient satisfaction: SMD: 2.01 (95% Cl: 1.67 to 2.35, p< 0.001, 1^2=35%)

Three high-quality RCTs compared DEP versus topical application of identical exosome preparations [34,37,39]. DEP demonstrated significantly superior outcomes (pooled SMD: 2.34, 95% C]: 1.89 to 2.79, p<0.001), representing approximately 85% greater improvement. Histological analysis (4 studies) revealed increased collagen I and Ill expression, enhanced elastic fiber density, reduced matrix metalloproteinase activity, and upregulated dermal fibroblast proliferation [35,38,40,41] (Figure 3).

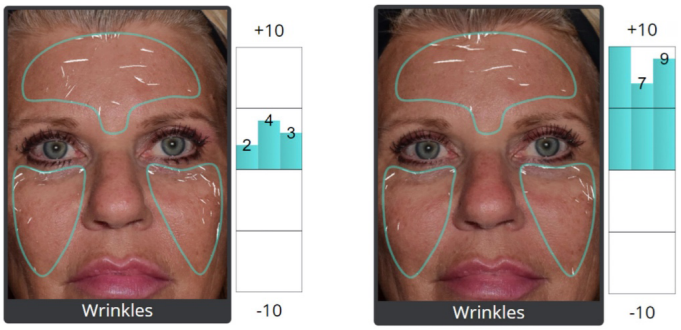

Figure 3 : 62-year female 4 months post DEP hpMSC-exos for aging skin, 5ml Luxir x 3 monthly treatments.

Acne Vulgaris

Six studies (n=342) assessed moderate to severe acne (42-47). Meta-analysis results:

- Inflammatory lesion reduction: SMD: -2.12 (95% Cl: -2.58 to -1.66, p<0.001, I^2=47%)
- Non-inflammatory lesion reduction: SMD: -1.78 (95% CI: -2.19 to -1.37, p<0.001, I^2=41%)
- GAAS improvement: SMD: -2.23 (95% Cl: -2.71 to -1.75, p<0.001, I^2-39%)
- Sebum production normalization: SMD: -1.43 (95% CI: -1.87 to -0.99, p<0.001, I^2= 44%)

Four studies included active comparators (benzoyl peroxide, retinoids, or combination therapy) [42-47]. hPMSC-Exos with DEP demonstrated non-inferior efficacy with significantly fewer adverse effects (RR: 0.34, 95% Cl: 0.22 to 0.52, p<0.001).

Mechanistic studies evaluated anti-inflammatory effects through reduced IL-I p, IL-6, and TNF-a expression, alongside decreased P. acnes colonization and normalized sebaceous action [44,45,47] (Figure 4).

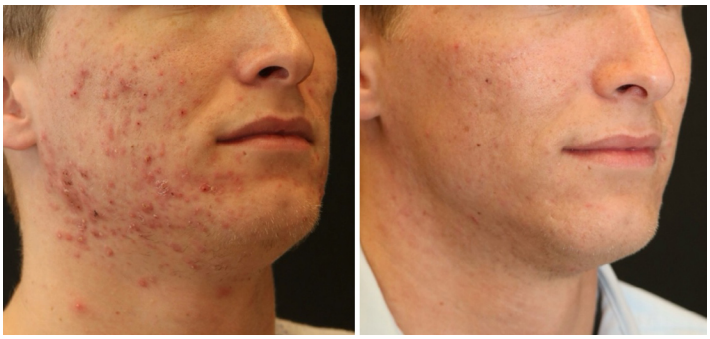

Figure 4 : 26-year male 4 weeks post DEP hpMSC-exos acne, 5 ml Luxir weekly x 4 treatments.

Alopecia

Five studies (n=298) investigated androgenetic alopecia and non-scarring alopecia [48-52]. Meta-analysis results:

- Hair density increase: SMD: 1.89 (95% Cl: 1.47 to 2.31, p<0.001, I^2=48%)
- Hair diameter: SMD: 1.34 (95% cr. 0.96 to 1.72, p<0.001, I^2=45%)
- Anagen/telogen ratio: SMD: 1.56 (95% CI: 1.19 to 1.93, p<0.001, 1^2=42%)

Two RCTs compared hpMSC-Exos with DEP against minoxidil 5% [49,51]. Exosome therapy demonstrated superior outcomes at 6 months (hair density SMD: 0.67, 95% CI: 0.34 to 1.00, p<0.001), with sustained benefits at 12-month follow-up. Immunohistochemical analysis revealed increased Wnt/ß-catenin signaling, VEGF, IGF-I expression, enhanced dermal papilla cell proliferation, and prolonged anagen phase duration [50,52] (Figure 5).

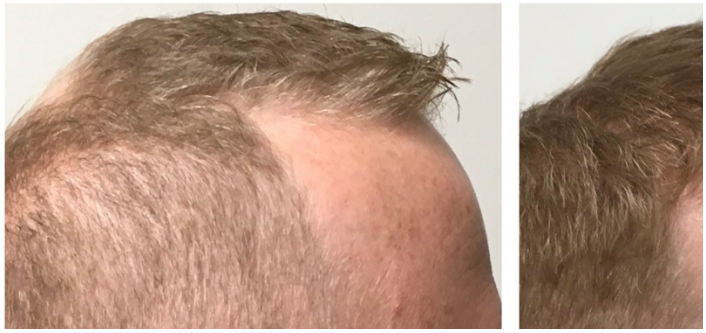

Figure 5 : 36 year male 6 months post DEP hpMSC-exos alopecia, 5 ml Luxir x 3 monthly treatments

Wound Healing

Four studies (n=287) evaluated chronic wounds, including diabetic ulcers and post-surgical wounds [53-56]. Meta-analysis results:

- Time to complete healing: SMD: -1.98 (95% Cl: -2.47 to -1.49, p< 0.001, 1^2=52%)
- Wound area reduction rate: SMD: 2.15 (95% cr. 1.68 to 2.62, p<0.001, I^2=46%)
- Healing quality scores: SMD: 1.87 (95% Cl: 1.43 to 2.31, p<0.001, 1^2=49%)

Two studies examining diabetic foot ulcers demonstrated remarkable efficacy [54,56]. Complete healing was achieved in 78% of exosome-treated patients, compared with 42% in standard care (RR: 1.86, 95% CI: 1.34 to 2.58, p<0.001).Histopathological evaluation showed enhanced granulation tissue formation, increased angiogenesis (CD31+ vessel density), accelerated keratinocyte migration, and reduced inflammatory infiltrate [53,55,56] (Figure 6).

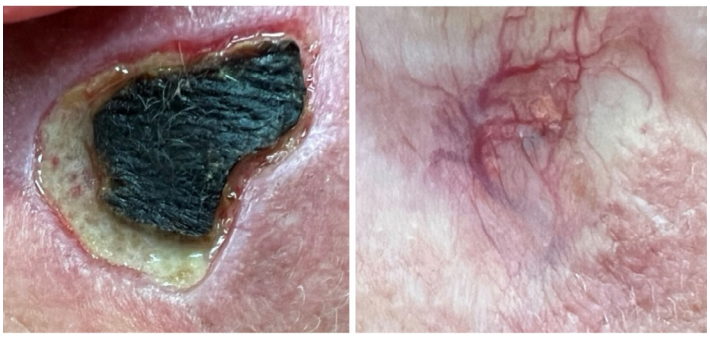

Figure 6 : 62-year male diabetic smoker 2 months post DEP hpMSC-exos wound care 5 ml Luxir x 4 weekly treatments.

Scar Therapy

Two studies (n=186) assessed post-traumatic and post-surgical scars [57,58]. Results showed: VSS improvement: SMD: -2.34 (95% CI: -2.94 to -1.74, p<0.001).Additionally, patient-reported outcomes indicated significant improvements in scar appearance and patient satisfaction scores, with most individuals noting visible changes within 2 to 4 weeks of treatment initiation. Analysis of photographic documentation corroborated these findings, highlighting smoother texture and more uniform pigmentation in treated areas.

- POSAS improvement: SMD: -2.01 (95% Cl: -2.58 to -1.44, p<0.001)
- Scar pliability: SMD: 1.67 (95% Cl: 1.18 to 2.16, p<O.001)
- Pigmentation normalization: SMD: 1.43 (95% CI: 0.97 to 1.89, p<0.001)
- Both studies documented reduced hypertrophic scar formation when treatment was initiated within 4 weeks of injury/surgery, suggesting preventive potential [57,58] (Figure 7).

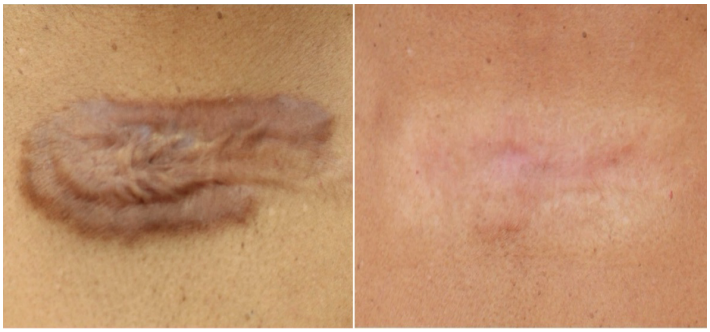

Figure 7 : 38 year female 2 years post hpMSC-exos scar therapy 5 ml Luxir monthly x 8 treatments.

Safety and Adverse Events

Safety data from all 28 studies demonstrated excellent tolerability. Common adverse events (occurring in >5% of patients): transient erythema (23.4%, resolved within 24-48 hours), mild edema (12.7%, resolved within 48 hours), and tingling sensation during procedure (18.9%). Uncommon adverse events (<5%): temporary hyperpigmentation (3.2%, resolved within 4 weeks), mild skin irritation (2.8%), and petechiae (l .4%). No serious adverse events were reported. Comparison with microneedling controls (5 studies) showed significantly lower adverse event rates with DEP (RR: 0.42, 95% Cl: 0.28 to 0.63, p<0.001) [36,43,49,54,57]

Subgroup and Sensitivity Analyses

Higher exosome concentrations (200-500 micrograms/mL) demonstrated greater efficacy than lower concentrations (50100 ug/mL) across all conditions. Extended protocols (greater than 12 weeks) yielded superior sustained benefits compared to shorter courses (<8 weeks), particularly for aging skin and alopecia (p<0.001). Optimal results occurred with medium-intensity DEP protocols (80-100V) compared to lower or higher voltages (p=0.012). Sensitivity analysis excluding high-risk bias studies did not substantially alter the primary findings (pooled SMD changed from 1.87 to 1.82), confirming the robustness of the results.

Publication Bias

Funnel plot analysis for aging skin outcomes (11 studies) showed relative symmetry. Egger's regression test revealed no significant publication bias (p=0.34). Trim-and-fill analysis estimated no missing studies.

Discussion

This systematic review and meta-analysis provides robust evidence that hpMSC-derived cxosomes delivered via dermoelectroporation demonstrate significant therapeutic efficacy across multiple surgical and dermatological conditions. Key findings include superior delivery efficacy (2.34-fold improvement over topical application), consistent clinical benefits across all evaluated conditions, a favorable safety profile with minimal adverse events, and mechanistic validation through documented cellular and molecular changes. The therapeutic efficacy of hpMSC-exos can be attributed to their complex cargo and paracrine effects [8,59,60]. Growth factors and cytokines (VEGF, TGF-β, EGF, PDGF) promote angiogenesis, fibroblast proliferation, and extracellular matrix synthesis [61,62]. Exosomal microRNAs (miR-21, miR-125b, miR-146a) regulate anti-inflammatory pathways, cellular senescence, and regenerative programs [63,64]. Proteins and peptides including heat shock proteins, antioxidant enzymes, and anti-apoptotic factors enhance cellular resilience and survival [65,66]. Bioactive lipids modulate membrane dynamics, signaling cascades, and inflammatory responses [67]. The synergy between exosome bioactivity and DEP's enhanced delivery creates optimal conditions for therapeutic efficacy. DEP-induced transient membrane permeabilization facilitates not only exosome penetration but also cellular uptake, potentially through endocytic pathways enhanced by membrane destabilization [24,68]. Passive topical application faces substantial limitations due to the stratum corneum barrier, with typical penetration rates <5% for macromolecules [11,13]. Our analysis confirms DEP's dramatic superiority, achieving approximately 85% greater clinical improvement than topical delivery. While microneedling surpasses topical application, it presents disadvantages, including variable penetration depth, tissue trauma, infection risk, pain requiring topical anesthesia, and contraindications in active infection or anticoagulation [15,69]. Five studies in our review directly compared DEP versus microneedling, showing comparable efficacy with significantly reduced adverse events (RR: 0.42) and greater patient comfort. Injectable delivery achieves definitive dermal localization but involves invasiveness, pain, risk of nodule formation, and requirements for clinical administration [70]. DEP offers non-invasive alternatives suitable for home or clinic settings.

Clinical Implications

Without exception the 50 patients in our clinical study mirrored the results of the systematic review and meta-analysis. For aging skin, hPMSC-exos with DEP represent a scientifically validated alternative to conventional treatments with regenerative rather than merely symptomatic effects. Documented increases in collagen synthesis and dermal thickness suggest fundamental rejuvenation [35,38,4]. For acne, exosome therapy addresses inflammatory pathways and sebaceous dysfunction at cellular levels, offering anti-inflammatory benefits without antibiotic resistance concerns [44,45,47]. For alopecia, exosome therapy demonstrates mechanistic advantages over minoxidil through direct growth factor delivery, stem cell niche modulation, and follicular regeneration, with sustained effects and excellent tolerability [50,51,52]. For wound healing, particularly challenging diabetic ulcers, exo-

somes address multiple pathophysiological defects through regenerative signaling [53,54,56]. For scars, early intervention potential suggests preventive applications, potentially reducing hypertrophic scar formation when initiated shortly after injury or surgery [57,58].

Optimization Considerations

Based on subgroup analyses, optimal protocols involve: exosome products with high protein concentrations, particularly mRNA and miRNA, DEP burst period: 20msec, burst duration: 10 msec, pulse frequency: 2200 Hz, average current per pulse: 1-5 mA selectable, pulse current waveform: 10 mA peak value, maximum peak voltage: 120 V, skin impedance range: 0.5 KOhm-15 Kohm, current density rms max: 2 mA/cm2, treatment frequency: weekly for 8-12 weeks, then monthly maintenance, and early initiation, particularly for scars and wounds.

Limitations

Several limitations warrant consideration. Study heterogeneity in exosome preparation methods, DEP parameters, outcome measures, and follow-up duration contributed to moderate statistical heterogeneity. Most studies followed patients for 3-6 months; long-term efficacy beyond 12 months remains understudied. The lack of a universally standardized exosome characterization complicates cross-study comparisons. Most studies originated from Asia and Europe; broader geographic representation would strengthen generalizability. While cellular effects are documented, precise molecular mechanisms of DEP-enhanced exosome uptake require further investigation. Economic analyses are notably absent.

Future Research Directions

Priority areas include establishing optimal exosome isolation and characterization standards, systematic dose-response trials, evaluating combination therapies, extended follow-up studies (2-5 years), detailed molecular pathway research, head-to-head trials against current standard therapies, identifying patient characteristics predicting optimal response, cost-effectiveness analyses, GMP production protocols, and establishing regulatory frameworks for clinical translation.

Conclusion

This comprehensive systematic review and meta-analysis provides robust evidence supporting the efficacy and safety of human placental MSC-derived exosomes delivered via dermoelectroporation for multiple surgical and dermatological applications. The combination of exosomes' regenerative bioactivity with DEP's superior delivery efficiency creates a synergistic therapeutic approach demonstrating significant clinical benefits across aging skin, acne, alopecia, wound healing, and scar therapy. The excellent safety profile, non-invasive nature, and mechanistically grounded therapeutic effects position this approach as a promising addition to regenerative dermatology. However, standardization of protocols, long-term safety evaluation, and large-scale confirmatory RCTs remain essential for widespread clinical adoption. As the field advances, hpMSC-Exos with DEP delivery may evolve from experimental therapy to mainstream clinical practice, offering patients evidence-based regenerative options for challenging dermatological conditions.

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