The therapeutic, diagnostic, and prognostic values of extracellular vesicles (exosomes) in dermatology: A systematic review

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The clinical exploration of extracellular vesicles (EVs, also called exosomes) in dermatology has recently grown, including cosmeceuticals. This systematic review aimed to collate existing clinical observations on EVs in dermatology for either therapeutic intervention or as a diagnostic or prognostic tool and to critically assess the degree of evidence of any observed feature. Primary studies that enrolled patients with dermatologic conditions and reported any role of EVs were included. Screening analysis, data extraction, and quality assessment were performed by 4 investigators. GRADE-CERQual, an adapted approach for the assessing the certainty of evidence qualitative sytematic reviews, was utilized to determine certainty and confidence for qualitative data. Outcomes included the therapeutic effectiveness of EVs' formulations, their safety, and any diagnostic potential. Fifty-two studies reporting data from 3066 patients were included. Methodologic inconsistencies, poor reporting, and low numbers of patients enrolled reduced the degree of certainty. The potential diagnostic and prognostic utilization of EVs were studied but have not been validated. EVs are being introduced into dermatology practices globally as cosmeceuticals. Observational studies have implied some therapeutic efficacy, but from a regulatory perspective, to our knowledge, no EV-based therapeutics has been approved in dermatology. Future clinical trials need to be randomized, double-blind, and placebo-controlled to support regulatory approvals, as diagnostic findings need to be supported by larger clinical cohorts. (JAAD Reviews 2024;1:135-74.)

Key words: alopecia; atopic dermatitis; exosomes; extracellular vesicles; melanoma; skin aging; systematic review.

INTRODUCTION

Dermatologic diseases are mediated by a wide variety of intercellular communication components, including extracellular vesicles (EVs).[1,2] Recently, EVs (also called exosomes) have been recognized as critical players in intercellular communication and are emerging as promising candidates for the management of several dermatologic diseases.[3-5] In addition, EVs are considered for both diagnostic and prognostic purposes in dermatology.[6,7] Specifically, there is a focus on utilizing mesenchymal stem cell (MSC)-derived EVs for therapeutic purposes in view of their broadly documented anti-inflammatory and tissue healing properties.[8-13]

Despite growing interest, a comprehensive systematic review of EVs in dermatology is absent. There

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is also a lot of interest in using EVs for cosmeceutical purposes, such as adjuvant topical therapy after laser and microneedling procedures.[14-16] Therefore, this review aimed to compile existing clinical observations of EVs in dermatology, regardless of whether the published report is focused on the therapeutic, diagnostic, or prognostic perspective of EVs. This review does not only evaluate available evidence but also aimed to identify areas of uncertainty or knowledge gaps and suggests future developments for EVs in dermatology.

MATERIALS AND METHODS

Databases and search strategy

This research was registered in PROSPERO (CRD42023477157) and followed the Meta-analysis of Observational Studies in Epidemiology and the Preferred Reporting Items for Systematic reviews and Meta-analyses reporting guidelines, as well as the Cochrane Handbook for Systematic Reviews of Interventions.[17-19] The review search strategy was composed of both Medical Subject Headings and nonofficial terms. A complete search strategy is available in Supplementary Appendix 1 (pp 3-5, available via Mendeley at https://doi.org/10.17605/OSF.IO/ZY8K9). We searched for publications in PubMed, Embase, Latin America and Caribean Health Sciences Literature, Cochrane Central Register of Controlled Trials, and Web of Science. In addition, ongoing clinical trials available at "*ClinicalTrials.gov*" and the "ITCRP platform" were tracked and considered to be potentially eligible for an updated version of this research. Searches were performed from November 3, 2023, to January 26, 2024.

Eligibility criteria

We considered publications eligible for inclusion if they enrolled patients diagnosed with a dermatologic pathology or condition, including acne, seborrheic dermatitis, psoriasis, atopic dermatitis (AD), systemic lupus erythematosus (SLE), systemic sclerosis, pigment dysregulation, vitiligo, and alopecia (areata and androgenetic). Furthermore, we included studies assessing the use of EVs in other cutaneous parameters, including skin aging, elasticity, and wrinkle improvement, as well as assessing their effectiveness in wound healing. The screening was performed by 4 independent assessors. Our inclusion criteria consisted solely of human-associated studies, regardless of study design. We excluded review articles but scrutinized their reference lists to ensure no primary study was missed. We used the definition of EVs and exosomes as defined by the International Society of Extracellular Vesicles.[20] Studies were eligible if they provided any report associated with EVs/exosomes based on their therapeutic, diagnostic, or prognostic roles. The results regarding the diagnostic and prognostic values of EVs are reported in the Supplementary Material (pp 10-18, available via Mendeley at https://doi.org/10.17605/OSF.IO/ZY8K9).

Data extraction and quality assessment

Four authors (TN, IJBN, LCVL, AHGM) independently extracted data from eligible publications using a standardized form created in Microsoft Excel. The outcomes and features collected are displayed within the disclosed Tables (Tables I[21-36] and II[28,32]). All 4 investigators (TN, IJBN, LCVL, AHGM) independently assessed the risk of bias in both randomized and observational studies. Disagreements were resolved through discussion involving a third reviewer author. The risk of bias in randomized trials was evaluated using the Cochrane Risk of Bias 2 tool,[37] cohort studies were appraised by the ROBINS-I tool,[38] and case reports and case series were evaluated using the methodology proposed by Murad et al.[39] Our criteria also included studies reporting on the diagnostic and/or prognostic relevance of EVs in the specified dermatologic disorders. Due to the unusual nature of these studies, a specific appraisal tool was required.[40] Considering the study designs, we used an adapted and validated risk of bias tool tailored for cross-sectional study assessments.[40]

Summary of findings and evaluation of the certainty of the evidence

Primary outcomes are reported in Table II,[28,32] which reports only data regarding the therapeutic role of EVs in the identified dermatologically prioritized agenda. We adhered to the adapted GRADE-CERQual, an adapted approach for the assessing the certainty of evidence qualitative sytematic reviews, guidance[41] to assess the confidence in the individual findings of qualitative evidence synthesis. The certainty of evidence was evaluated by 2 assessors (TN and IJBN), taking into account the risk of bias, inconsistency, imprecision, indirectness, and publication bias.

RESULTS

Overall findings

In general, our search retrieved 46 primary studies[21-23,25,26,29-36,42-73] and 6 additional relevant and published clinical reports[24,27,74-77] from external resources (not primarily retrieved from our search on the predefined databases). The full review flowchart is shown in Fig 1. We identified 14 ongoing clinical

Table I. Summary of major clinical effects from included studies as well as reported adverse events of interventions

Study ID	Intervention description and composition	Major findings summary
Chernoff et al[21]	Exosome biostimulation through infusion was by 1. Facial exosome biostimulatory infusion was followed immediately by dilute CaHA (dilution 1:1) injection to the face; 2. Exosome biostimulatory dermal infusion was followed immediately by hyperdiluted CaHA (dilution 1:4) injection to the neck; 3. Injection of dilute CaHA (dilution 1:1) to the face without exosomes; or 4. Injection of hyperdiluted CaHA (dilution 1:4) to the neck without exosomes.	1. Results revealed 16 of 20 dermal infusion patients to be very satisfied with the results 2. Four of 20 reported being satisfied 3. There were no dissatisfied reports 4. Patients in the infusion group were uniformly pleased that there was no pain associated with the treatment 5. All dermal infusion patients and CaHA injection patients alone showed an improvement in the tone, quality, and clarity of their skin with a reduction in fine lines, pores, pigment oiliness, and an improvement in texture and vascularity. 6. Patients who had dermal infusions immediately prior to CaHA injections displayed an earlier and more enhanced response than the CaHA facial injections alone at 30 days.
Cho[22]	ASCE was topically applied in combination with iontophoresis	1. ASCE could reduce or modulate overreactive inflammation in the skin in an atopic dermatitis model 2. The AD score was significantly improved up to 30% in a dose-dependent manner 3. Further, major proinflammatory cytokines, including IL-4, IL-13, TLSP, and others, were downregulated by up to 30% -50% in a dose-dependent manner. 4. ASCE could promote, by 40%-70% in a dose-dependent manner, the de novo synthesis of ceramides and dihydroceramides, key lipid molecules in skin barrier formation, which led to the significant improvement of the skin barrier disruption model.
Cho[23]	ASCE was topically applied in combination with microneedling for 6 months	1. After 6 months of 10 microneedling sessions, our clinical study revealed an increase of 9 hairs per 1 cm^2, rising from a baseline of 180 to 189. 2. The ASCE formulation demonstrated significant improvement in clinical cases of both androgenic alopecia and alopecia areata.
Gibello et al[24]	Participants undergo a blood sample for s-EV isolation and the preparation of 6 doses of active s-EVs. The CVU with a bigger surface was treated with s-EVs and standard wound dressing, while the smaller one had standard wound dressing alone (sham). A multilayer bandage was made to guarantee homogeneous elastic compression throughout the limb. Medications were renewed 3 times per week for 2 weeks.	1. Lesions treated with s-EVs displayed a higher percentage of granulation tissue compared with the sham group, with 3 out of 5 s-EV-treated lesions showing 75%-100% granulation tissue, while sham lesions showed none. 2. A higher reduction of sloughy tissue was observed in s-EV-treated lesions at the end of treatment, and this reduction increased further at day 30. 3. s-EV treatment led to a median surface reduction of 151 mm^2 compared with 84 mm^2 in the sham group. The difference was more pronounced at day 30, with s-EVs resulting in a surface reduction of 385 mm^2 compared with 106 mm^2 in the sham group ($P = .004$). 4. Histological analyses revealed regenerative tissue with an increase in microvascular proliferation areas, consistent with the enrichment of TGF-β1 in s-EVs.

Continued

Table I. Cont'd

Study ID	Intervention description and composition	Major findings summary
Han et al[25]	Once a day, reagents were smeared on the face and the inside of the arm of the volunteers.	1. Results showed that the brown spots, UV spots, wrinkles, speckles, and red zones improved remarkably in the volunteers treated with PL. 2. Compared with the control group, the brown spots and UV spots of the PL-treated group were reduced, indicating that PL displayed a significant improvement in the pigmentation caused by UV irradiation. 3. The percentage of wrinkles, speckles, and red zones in the PL-treated group significantly improved, indicating that PL may be beneficial in delaying aging and reducing the potential inflammatory reaction of volunteers' skin. 4. The results showed that the increase in collagen density after PL treatment was higher than that in the control group. 5. Thus, PL demonstrated good antiaging and antiinflammatory effects on the volunteers.
Han et al[26]	ASCE was topically applied with SRLV-S of lyophilized human ASCE for 5 consecutive weeks.	1. The average IGA score decreased from week 2 and continued to decrease until week 12. 2. A total of 12 out of 20 (60%) patients achieved an IGA score of 1, almost clear at least once during the entire clinical trial period. 3. The average CEA score decreased from the first week after the first exosome treatment. 4. A total of 11 out of 20 (55%) patients achieved a CEA score of 1 at least once during the entire clinical trial period. 5. The average subject satisfaction score was highest in week 2 and slowly decreased over time. 6. A total of 19 patients (95%) were satisfied with the treatment. 7. Compared with baseline, the erythema index at week 4 decreased by 31, 27, 13, and 25 units on the forehead, chin, right, and left cheek, respectively. 8. The analysis of stratum corneum samples revealed the expression of IL-1α and human thymic stromal lymphopoietin was suppressed after exosome treatment, whereas filaggrin and vascular endothelial growth factor expression increased.

Johnson et al[27]	Each patient underwent a randomized allocation process wherein one arm received a subcutaneous injection of LEAP-isolated pEVs formulated as a clinical-grade, allogeneic therapeutic product designated as the treatment wound. The other arm, designated as the comparator wound, received a subcutaneous injection of a placebo formulation	1. Particle analysis revealed 8.71 $\pm$ 2.75 $\times$ 10^{11} pEVs with a size range of 65 $-$400 nm 2. Western blot showed enrichment of EV markers (CD9, CD63, syntenin) and absence of negative marker (calnexin) 3. Identified 928 proteins, including EV biomarkers, platelet membrane proteins, glycoproteins, and growth factors (IGF, TGF-ß). Proteins were annotated under categories of Molecular Function, Biological Processes, and Subcellular localization. 4. Exoria-labeled pEVs successfully associated with NHDFs after 2-4 h of incubation. 5. pEV-treated NHDFs showed increased proliferative capacity and enhanced migration. 6. pEVs increased the angiogenic potential of HDMECs. 7. pEVs induced phosphorylation of ERK and Akt signaling pathways in NHDFs. 8. Clinical pEV-treated wounds healed successfully without abnormal scarring. 9. All participants achieved wound closure on day 30.
Kwon et al[28]	Patients received 3 consecutive treatments of FCL on their whole face at an interval of 3 weeks, with a follow-up evaluation 6 weeks after their final treatment session.	1. A significant reduction in the ECCA score from baseline was observed on the ASCE side beginning at the first posttreatment visit and on the control side from the second posttreatment visit. 2. The difference in percent reduction of ECCA score between the 2 regimens was significant at the second posttreatment visit. 3. The ECCA score was reduced by 32.5% (95% CI, 24.8%-40.2%) from baseline on the side treated with ASCE. 4. The ECCA score had a reduction of 19.9% (95% CI, 12.2%-27.6%) on the control side ($P < .01$). 5. The ASCE-treated facial side demonstrated superior improvement based on the IGA score compared with the control side after 3 sessions of each treatment ($P = .02$). 6. Sixteen out of 25 facial sides achieved grade II or more improvements on the ASCE side compared with 12 on the control-treated sides.

Continued

Table I. Cont'd

Study ID	Intervention description and composition	Major findings summary
Lu et al[29]	MK-Exo was smeared on the facial skin of female volunteers twice a day for 28 days without using other cosmetics.	1. MK1-Exo demonstrated the capability to increase filaggrin by approximately 3-fold, and CD44, the receptor of hyaluronic acid, by over 60%. 2. MK-Exo decreased the level of AQP3 at relatively high concentrations. 3. MK-Exo may work as moisture by inducing the expression of FLG and CD44 in keratinocytes without a change in AQP3 expression. 4. The preliminary result suggested that MK-Exo also might function across the species on the human skin fibroblasts. 5. MK-Exo increased the level of hyaluronidase 2 by more than 2 times. 6. MK-Exo also enhanced fibroblast cell migration, specifically in contrast to keratinocytes. 7. These results suggested that MK-Exo may play the role of antiwrinkling by reducing collagen degradation and improving cell migration. 8. The results indicated the absence of sensitization and irritant potential of MK-Exo on both animal and human skin. 9. The skin moisture content increased by 4.64% on day 14 and 5.6% on day 28 across all cohorts. The increase in moisture content was higher in the volunteers aged 36-45 years, while the increase in volunteers aged 26-35 years was not statistically significant. 10. The skin brightness also dramatically increased on day 28 11. MK-Exo could also improve fibroblast cell migration instead of keratinocytes 12. More than 90% satisfy the moisturizing effect of MK-Exo 13. The results indicated that MK-Exo has the function of moisturizing 14. The F3/F4 and R2 values increased by 6.33% and 7.24% on day 28, respectively, with a higher increase of 10.74% in the cohort aged 36-45 years. 15. All results indicated that MK-Exo was safe and may moisturize and antiwrinkle by improving the expression of FLG, CD44 in keratinocytes, and HAS2 in fibroblasts, enhancing cell migration and inhibiting the UV-induced reduction of collagen in fibroblasts.
Norooznezhad et al[30]	The patient is a candidate for treatment with allogenic human MSC-derived EVs for 3 sessions.	1. She was followed for 10 months and demonstrated hair growth up to 8 to 9 cm, and no adverse event was observed. 2. The results were clinically promising and satisfactory for both the patient and the treatment team.

Park et al[31]	The treatment course consisted of repeated application of more than 6×10^{10} particles/vial of ASC-exosome on the scalp area with a microneedle roller once per week for 12 consecutive weeks.	1. The use of ASC-exosomes for 12 weeks resulted in statistically significant improvements in both hair density and thickness. 2. Mean $\pm$ SD hair density increased from 121.7 $\pm$ 37.2 to 146.6 $\pm$ 39.5 hairs/cm^2 ($P < .001$), and mean $\pm$ SD hair thickness increased from 52.6 $\pm$ 10.4 to 61.4 $\pm$ 10.7 μm ($P < .001$). 3. There was no observed correlation between patient age and changes in hair thickness or density (age and hair thickness, $P = .706$; age and hair density, $P = .342$). 4. The duration of hair loss did not correlate with treatment response (disease duration and hair thickness, $P = .584$; disease duration and hair density, $P = .128$). 5. None of the patients reported severe adverse reactions, irritation, or itching.
Park et al[32]	Each participant washed their entire face with mild soap, and 30 min before treatment, an eutectic mixture of local anesthetics cream was applied with occlusion for topical anesthesia. Next, 2 mL of normal saline solution was mixed with a vial of ASCE + Derma SRLV-S to prepare a HACS. The HACS was topically applied to the one-half face, followed by microneedling at a depth of 1 mm. The other half face was treated with 2 mL normal saline solution followed by microneedling	1. At the final follow-up visit, the mean percent reductions in Ra, Rt, and Rz were 12.4%, 14.4%, and 13.4%, respectively, in the HACS group and 6.6%, 6.8%, and 7.1%, respectively, in the control group. 2. The difference between the 2 treatments was not significant at week 3 but became statistically significant at week 6. 3. At the final follow-up visit (week 12), for the HACS group, 46% had a GAIS score of 3, 14% scored 4, and 14% scored 5. In contrast, in the control group, 46% scored 3, 7% scored 4, and 7% scored 5. 4. An increase in skin elasticity was consistently observed in the HACS group at every assessment point compared with baseline, while there was no significant improvement in the control group during the study. 5. At week 12, skin elasticity increased by an average of 11.3% from baseline in the HACS group but decreased by 3.3% in the control group. 6. Skin hydration in the HACS group continued to increase until week 12, with an average increase of 6.5% at the last follow-up visit, significantly greater than the 4.5% increase observed in the control group at week 12. 7. At the final follow-up evaluation, the average decrease in the melanin index was 9.9% in the HACS group and 1.0% in the control group. 8. Histological specimens from the HACS-treated group at the final follow-up revealed higher collagen and elastic fiber density, along with increased deposition of mucin and newly synthesized collagen compared with baseline. 9. Similar histological changes were observed in the control group, although they were less prominent than those in the HACS group. These findings collectively demonstrate the effectiveness and safety of the combined treatment using HACS and microneedling for addressing facial skin aging.

Continued

Table I. Cont'd

Study ID	Intervention description and composition	Major findings summary
Proffer et al[33]	The morning and evening skincare routine included Vanicream Gentle Facial Cleanser, Intensive Repair Serum, and EltaMD UV Daily Broad-Spectrum SPF 40 or Vanicream Lite Lotion (morning) and EltaMD PM Therapy Facial Moisturizer or Vanicream Lite Lotion (evening) for 6 weeks	1. Fine lines and wrinkles showed an average improvement of 0.3 and 0.1 points, respectively, between baseline and 6 weeks. 2. No visible improvement was observed in skin sagginess. 3. Skin texture, radiance, and firmness demonstrated average improvements of 0.3, 0.4, and 0.1 points, respectively. 4. The overall appearance improved by 0.3 points across the entire participant cohort. 5. Representative images from a 49-year-old female participant indicated a reduction in redness based on the investigator's review. 6. Hemoglobin concentration decreased in high intensity/contrast red areas at 6 weeks compared with baseline. 7. In the top quartile analysis (n = 14) focusing on the maximal response from topical platelet-derived exosomes, there was a statistically significant mean $\pm$ SD reduction of -2.39 ± 2.68 (P = .005) in erythema fractional area at 6 weeks compared with baseline. 8. A statistically significant mean $\pm$ SD reduction of -0.0161 ± 0.005 ($P \leq .0001$) was observed in the brown spot fractional area at 6 weeks. 9. Color intensity (luminosity) demonstrated a statistically significant mean $\pm$ SD improvement of 5.42 ± 1.36 ($P \leq .0001$) at 6 weeks compared with baseline in the top quartile cohort (n = 14). 10. Color evenness units showed a statistically significant mean $\pm$ SD improvement of 0.071 ± 0.03 ($P \leq .0001$) at 6 weeks compared with baseline. 11. There was a statistically significant mean $\pm$ SD reduction of 0.01 ± 0.009 (P = .0023) in static wrinkle units in the forehead fractional area. 12. A statistically significant mean $\pm$ SD improvement of 224.2 ± 112.8 ($P \leq .0001$) was observed in the skin health score.

Sasaki[34]	Approximately 0.08 to 0.1 mL was deposited in the intradermal plane at each dot, from which an estimated spread of solution up to 2.5 cm of the solution was anticipated	1. After a single XoFlo treatment, 20 female patients, predominantly between 50 and 70 years old, exhibited either hair growth or stable maintenance of hair density. 2. Two female patients (aged 38 and 59 years) reported progressive hair loss after the XoFlo treatment. 3. Among 9 male patients aged 20-70 years, most responders were between 20 and 50 years old, demonstrating either hair growth or stable maintenance after a single XoFlo treatment. 4. Two female patients experienced progressive hair loss despite receiving various FDA-approved and other hair loss drugs. 5. A 38-year-old patient with over 10 years of alopecia showed no response to combination therapy of 4 drugs over 5 years and later to 4 sessions of platelet-rich plasma treatments while on spironolactone and dutasteride medications. 6. Thirteen female patients with less than a 7-year history of alopecia demonstrated either hair growth or stable maintenance after a single XoFlo treatment. 7. A smaller number of female patients with over 10 years of hair loss still experienced either hair growth or maintenance after treatment. 8. The most consistent increases in percent change in hair densities (11.1%-24.2%), terminal hair densities (16.4%-45.5%), vellus hair densities (18.4%-36.4%), and follicle diameter (9.4%-32.3%) were observed in the frontal-temporal scalp, with the least change in the occipital scalp. 9. Trichoscans at 6 months showed no significant change or hair loss after treatment in 3 female and 1 male patient. 10. Percent changes from baseline in hair density (−1.6% to +5.3%), terminal hair density (−3.4% to +3.3%), vellus hair density (−5.1% to +1.7%), and follicle diameter (−5.3% to +4.6%) consistently remained below percent changes in the occipital region (8.7% to 15.8%). 11. Among the 22 female patients, 2 remained "very dissatisfied," 8 were "satisfied," and 12 were "very satisfied" with their results. Out of the 9 male patients, 1 remained "dissatisfied," 5 were "satisfied," and 3 were "extremely satisfied" with their treatments.

Continued

Table I. Cont'd

Study ID	Intervention description and composition	Major findings summary
Wang et al[35]	Each patient received 4 treatments at 1-month intervals	1. In the clinical application study, groups B, C, and D demonstrated significantly improved therapeutic effects and patient satisfaction compared with group A ($P < .05$). There was no significant difference among groups B, C, and D. 2. Patients in group B reported higher pain levels compared with those in the other 3 groups. 3. Patients in group D reported a better treatment experience 4. Human umbilical cord mesenchymal stem cell-derived exosomes were found to safely and effectively improve the symptoms of melasma. 5. Nonablative fractional laser and polydioxanone bioabsorbable skin mesh, compared with microneedles, also demonstrated a good effect in promoting penetration. These findings are deserving of further exploration and consideration for clinical application.
Ye et al[36]	All volunteers applied 1 mL to the face twice a day (morning and evening) after thawing the product into a liquid state and stopped using their own facial moisturizers. After thawing or unsealing, the product should be stored at 2 to 8 °C and used up within 24 h.	1. Objective symptoms, including roughness, scales, erythema, and subjective symptoms like tension, burning, or itching, significantly decreased on days 7, 14, and 28 compared with baseline after using the product. 2. Scores of dryness significantly decreased on days 7, 14, and 28 compared with baseline after using the product. 3. On days 7, 14, and 28 after product use, both objective and subjective symptoms showed improvement, with percentages of 33.3%, 29.6%, and 44.4%, respectively. 4. Dryness symptoms demonstrated improvement on day 7 (45.8%) and a significant improvement on days 14 and 28 (75.0% and 83.3%, respectively). 5. The skin a* value significantly decreased on days 14 and 28 after using the product compared with baseline. 6. Lactic acid stinging test scores significantly decreased on days 7, 14, and 28 after using the product compared with baseline. 7. Skin sebum significantly decreased on day 14 after using the product compared with baseline. 8. Skin surface pH value significantly increased on day 28 after using the product compared with baseline. 9. Although no significant difference was observed in skin TEWL and hydration at each time point after using the product compared with baseline. The proportions of subjects very satisfied with the product use experience via questionnaires were 75% on day 7, 75% on day 14, and 80% on day 28.

AD, Atopic dermatitis; *AQP3,* Aquaporin 3; *ASC*, adipose stem cell; *ASCE*, adipose stem cell exosome; *Caha*, calcium hydroxylapatite; *CEA*, clinical erythema assessment scale; *CVU*, cardiovascular unit; *ECCA*, *Échelle d'évaluation Clinique des Cicatrices d'Acné*; *ERK*, extracellular-regulated kinase; *EV*, extracellular vesicle; *FCL*, fractional CO2 laser; *FDA*, Food and Drug Administration; *FLG*, filaggrin; *GAIS*, Global Aesthetic Improvement Scale; *HACS*, human ASCE-containing solution; *HAS2*, hyaluronidase 2; *HDMECs*, human dermal microvascular endothelial cells; *IGA*, Investigator's Global Assessment score; *IGF*, insulin-like growth factor; *IL,* interleukin; *LEAP*, ligand-based exosome affinity purification; *MK-Exo*, MK-derived exosomes; *MSC*, mesenchymal stem cell; *NHDF*, normal human dermal fibroblasts; *pEV*, platelet derived extracellular vesicles; *PL*, Phellinus Linteus exosome-like; *Ra*, average roughness; *Rt*, maximum height of the roughness profile; *Rz*, average roughness; *s-EVs*, serum-derived EVs; *SRLV*, signal skin rejuvenation lyophilized vial; *SRLV-S*, signal skin rejuvenation lyophilized vial; *TEWL*, trans-epidermal water loss; *TGF*, transforming growth factor; *TSLP*, thymic stromal lymphopoietin.

Table II. Summary of findings and certainty of the evidence for included studies analyzing the therapeutic role of extracellular vesicles in several dermatologic diseases and conditions

	Certainty of the evidence (GRADE)					
Outcome (no. of systematic reviews)	**Methodological limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality**
Alopecia						
Extracellular vesicles demonstrated positive outcomes in terms of hair density, thickness, and patients' satisfaction (*n* = 4 studies; 100 patients)	Critical*	Not serious†	Not serious‡	Serious§	Moderate‖	Very low¶
Skin aging, skin rejuvenation, and skin-related parameters						
From a combination of protocols and formulations, extracellular vesicles demonstrated potential in addressing specific skin concerns and enhancing overall skin health (*n* = 7 studies; 292 patients)	Critical#	Not serious†	Not serious‡	Serious§	Moderate‖	Very low¶
Atopic dermatitis						
Extracellular vesicles are suggested to have a dose-dependent reduction in AD score, downregulation of proinflammatory cytokines, and promotion of ceramide synthesis (*n* = 2 studies; 50 patients)	Critical*	Not serious†	Not serious‡	Serious§	Moderate‖	Very low¶
The therapy with extracellular vesicles showed improvement in IGA and CEA scores, high patient satisfaction, and positive modulation of biomarkers, showcasing efficacy in atopic dermatitis management (*n* = 2 studies; 50 patients)						
Wound healing						
Therapy based on extracellular vesicles facilitates the reduction in sloughy tissue, promotes regenerative tissue with increased microvascular proliferation, and enhances the successful of wound closure (*n* = 2 studies; 20 patients)	Critical#	Not serious†	Not serious‡	Serious§	Moderate‖	Very low¶
Acne						
The utilization of exosomes with fractional CO_2 laser provides synergistic effects on both the efficacy and safety of atrophic acne scar treatments (*n* = 1 study; 25 patients)	Critical**	Not serious†	Not serious‡	Serious§	Unclear††	Very low‡‡

Continued

Table II. Cont'd

Outcome (no. of systematic reviews)	Certainty of the evidence (GRADE)					
	Methodological limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality
Melasma						
Extracellular vesicles are safe and effective in improving melasma symptoms (n = 1 study; 60 patients)	Moderate[§§]	Not serious[†]	Not serious[‡]	Serious[§]	Unclear[i]	Low[‖‖]

Note: "Low certainty" by the GRADE Working Group grades of evidence is the summary rating of the included studies and provides some indication of the likely effect. The likelihood that the effect will be substantially different is high. "Very Low" certainty is the summary rating of the included studies that do not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.

AD, Atopic dermatitis; *CEA*, clinical erythema assessment scale; *GRADE*, Grading of Recomendations Assesment Development and Evaluation; *IGA*, Investigator's Global Assessment score.

*Methodological limitations were primarily related to lack of control to confounding bias, bias in the classification of interventions, bias in the measurement of outcomes, and bias in the selection of participants into the study.

[†]Inconsistency judged by evaluating the consistency of the direction and primarily the difference in the magnitude of effects across studies (since statistical measures of heterogeneity are not available). As we did not find differing results for each outcome across the included studies, we considered a "not serious" risk for inconsistency.

[‡]The participants in the included studies were, in general, a clinically representative sample matching the inclusion criteria; therefore, we did not have any significant concerns about the appropriateness of participants identified in the review.

[§]Downgraded because of the limited number of patients in included studies (against the optimal information size).

[‖]Although a funnel plot visualization graph was not created, we inferred that the existence of studies focusing only on positive results of exosomes and extracellular vesicles for the determined disease or dermatologic condition might be associated with a publication bias (which would be visible as a graphical asymmetry, if performed).

[¶]Downgraded due to methodological limitations, imprecision, and publication bias.

[#]Methodological limitations were primarily related to lack of control to confounding bias, bias in the classification of interventions, bias in the measurement of outcomes, bias in the selection of participants into the study, issues in the randomization process (such as in Park et al[32]), missing outcome data (such as in Park et al[32]), and selection of reported results (such as in Park et al[32]).

**Methodological limitations associated with the randomization process, missing outcome data, and selection of reported results (as reported in Kwon et al[28]).

[††]Downgraded due to methodological limitations and imprecision.

[‡‡]We decided to judge the publication bias for the acne study as this was the only available study covering the applicability of exosomes and extracellular vesicles for this disease.

[§§]Methodological limitations were primarily related to bias in the measurement of outcomes.

[‖‖]Downgraded due to methodological limitations, imprecision, and publication bias.

trials that have a potential association with our systematic review for future analysis. The list of these studies is provided in Supplementary Material 2 (pp 6, available via Mendeley at https://doi.org/10.17605/OSF.IO/ZY8K9).

The objectives of the included studies reflect a broad evaluation of EVs in dermatologic disorders, including their use as therapeutics, diagnostics, and prognostics. We evaluated EVs in multiple dermatologic conditions, ranging from psoriasis,[44,45,50,52,62,70,73] SLE,[47,51,55,62,65,67,69,71] vitiligo,[48,53,54,56] alopecia,[23,30,31,34] systemic sclerosis,[46,63,68,69] AD,[22,26,43,58,60,64,72] melanoma,[49,74-77] and the aging process of the skin,[21,25,29,32,33,36] melasma,[35] and burn injuries.[57] Additionally, safety studies were also included in the analysis. The main objective of each assessed study is provided in Table III.[21-36,42-77]

The primary studies encompassed a diverse geographic distribution, mostly including prominent contributions from Asia, including China (n = 15; 28.8%) and South Korea (n = 6; 11.5%). The main characteristics of the included primary studies are available in Table III. Our collated data from 3066 individuals included both patients with specific dermatologic conditions as well as healthy individuals (characteristics described in Table IV[21-36,42-77]). The primary studies utilized several research designs, including observational cross-sectional studies, functional in vitro evaluations (n = 36; 69.2%),[22,29,42-50,53,55-61,63,65-77] observational cohorts (n = 12; 23.0%),[21,23,25,26,29,31,33-36,62] case reports or case series (n = 3; 5.7%),[24,30,64] and 3 randomized clinical trials.[27,28,32]

Risk of bias and quality assessment

The assessment of reporting quality and risk of bias in the observational cross-sectional studies were essentially critically assessed due to bias associated with control of confounders, participant selection,

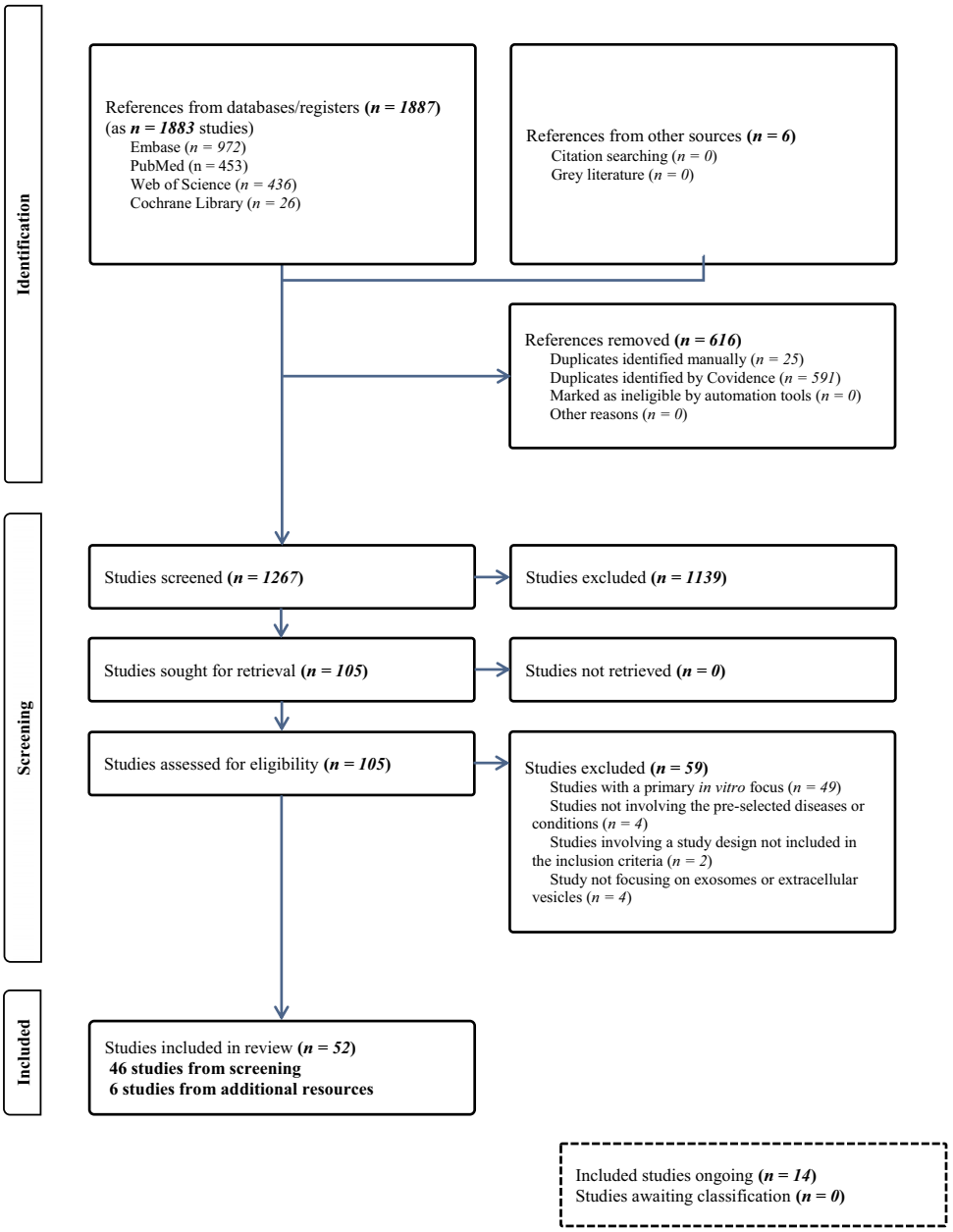

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses and Meta-analysis flowchart diagram.

outcome measurements, and classification of interventions. Additionally, the quality of observational cohorts achieved scores ranging from 0 to 6, which is considered low, with most drawbacks related to sample size, lack of definition of dose-related effects, and lack of evaluation of the impact of potential confounders. The risk of bias among randomized clinical trials was deemed to be high in all studies due to potential issues for the randomization process, missing outcome data, measurements of the outcomes, and selection of reported results. The evaluation of all studies, including the case reports and evaluation of case series, are represented in Table V.[21-23,25,26,28-39,42-55,57-77,81,82]

Therapeutic-related studies

Alopecia. Four studies have been published using EVs in the treatment of alopecia, reporting diverse outcomes.[23,30,31,34] For instance, Norooznezhad et al[30] reported a case of a complete regrowth of terminal hair in a case of persistent chemotherapy-induced alopecia after receiving human placenta MSC-derived EVs through subcutaneous scalp injections. Likewise, a retrospective open-

Table III. Identification characteristics among included studies

Author ID	Journal	Journal impact factor (2022)	Condition or disease approached	Objective	Country
Baniel et al[42]	Journal of Investigative Dermatology	6.5	DM	The purpose of this study was to characterize the protein content of plasma-derived EVs in DM and explore their role in disease pathogenesis.	NA
Chang et al[43]	Clin Cosmet Investig Dermatol	2.3	AD	To investigate the diversity of plasma EVs collected from AD patients and healthy individuals; suggested that the candidates for uniquely or differentially expressed proteins in plasma EVs could be a diagnostic marker in AD.	China
Chen et al[45]	Discov Med	1.4	Psoriasis	To identify the common mechanisms among PsA, psoriasis Bulgaria's, rheumatoid arthritis, and gouty arthritis	China
Chen et al[44]	Frontiers in Medicine	3.9	Psoriasis	To describe the levels of plasma exosomal miRNAs in PsV patients and analyze the functional features of differently expressed miRNAs and their potential target genes for the first time.	China
Chernoff et al[21]	Journal of Cosmetic Dermatology	2.3	Skin biostimulation	To develop safe, reproducible methods of improving topical exosome absorption to enhance the quality either by themselves or in combination with injectable CaHA.	NA
Cho[22]	Journal of Investigative Dermatology	6.5	AD	To determine if ASCE can attenuate severe inflammation and promote skin barrier reconstruction in the AD model.	NA
Cho[23]	Journal of Investigative Dermatology	6.5	Alopecia	To evaluate the safety and efficacy of the exosome-based formulation derived from allogeneic adipose tissue MSCs for androgenetic and areata alopecia.	South Korea
Chouri et al[46]	Journal of Autoimmunity	12.8	SS	To investigate the miRNA signature in the serum of SS patients and further assess their expression in the early stages of the disease.	Netherlands and Italy
Crescitelli et al[74]	Journal of Extracellular Vesicles	16	Melanoma	To establish a method to isolate and categorize subpopulations of EVs isolated directly from tumor tissue.	Sweden
Crescitelli et al[75]	Frontiers in Cell and Development Biology	5.5	Melanoma	To compare the results of tumor tissue DNA and plasma	Sweden

Dong et al[47]	Biomed Res Int	3.246*	SLE	To investigate the effects and potential mechanisms of serum exosomes-derived miRNAs on BMMSC senescence in SLE.	China
Doss et al[48]	Journal of the Egyptian Women's Dermatologic Society	NA	Vitiligo	To clarify the suggested role of lncRNA H19 and miRNA let7a derived from human skin exosomes in vitiligo pathogenesis.	Egypt
Gibello et al[24]	Pharmacological Research	9.3	Wound healing	To evaluate the healing properties of autologous s-EVs in CVU patients resistant to conventional treatments.	Italy
Guo et al[49]	Cancer Cell International	5.8	Melanoma	To identify the differential miRNAs, determine the diagnostic efficiency, and detect the biological behavior of melanoma cells.	China
Han et al[25]	J Nanobiotechnology	10.2	Skin aging	To explore the efficacy and molecular mechanisms of PL in resisting skin photoaging.	South Korea
Han et al[26]	J Dermatolog Treat	2.9	AD	To evaluate the efficacy and safety of ASCEs in DFR	South Korea
Jacquin-Porretaz et al[50]	Acta Derm Venereol	3.6	Psoriasis	To investigate the involvement of exosomes in psoriasis	France
Jang et al[76]	Journal of Extracellular Vesicles	16	Melanoma	To determine the diversity of EVs specifically in this tissue	NA
Johnson et al[27]	Journal of Extracellular Vesicles	16	Wound healing	To provide the first evidence for the safety and therapeutic utility of clinical-grade pEVs to humans.	Australia
Karlsson et al[51]	J Autoimmun	12.8	SLE	To study the exposure of both pCRP and mCRP on EVs in SLE plasma and the implications of each in disease activity, organ damage, and clinical manifestations.	Sweden
Kwon et al[28]	Acta Derm Venereol	3.6	Acne	To evaluate the clinical efficacy and safety of ASCE as an adjuvant therapy after the application of FCL for acne scars.	South Korea
Lättekivi et al[52]	Int J Mol Sci	5.6	Psoriasis	To compare the miRNA contents and surface proteome of the EVs in the blood serum of PsV and PsA patients to HCs.	Estonia, Denmark, and UK
Li et al[55]	Clinics (Sao Paulo, Brazil)	2.7	SLE	To investigate the clinical value of serum exosomal miRNAs in SLE	China
Li et al[53]	J Invest Dermatol	6.5	Vitiligo	To identify the expression profile of circulating exosomal miRNAs and investigate their role in the pathogenesis of SV.	China

Continued

Table III. Cont'd

Author ID	Journal	Journal impact factor (2022)	Condition or disease approached	Objective	Country
Liu et al[54]	J Invest Dermatol	6.5	Vitiligo	To evaluate and identify the significance of miRNAs in exosomes extracted from the sera of active vitiligo patients.	NA
Lu et al[29]	bioRxiv	NA	Skin aging	To investigate the novel roles of bovine MK-Exo on human skin antiaging and to analyze the antiaging effect of MK-Exo on humans, human keratinocytes, HaCat, human fibroblasts, and CCC-ESF-1, and the primary safety evaluation of MK-Exo on skin.	USA
Luo et al[56]	Clinical, Cosmetic, and Investigational Dermatology	2.3	Vitiligo	To use serum exosomal miRNAs as a reference for evaluating vitiligo progression.	China
Maile et al[57]	International Journal of Molecular Sciences	5.6	Burn injury	To investigate if EVs after burn injury promote macrophage activation and if EV contents can predict the length of hospital stay.	USA
Meng et al[58]	Experimental and Therapeutic Medicine	2.7	AD	To elucidate the role of exosomal transfer RNA-derived fragments in AD as potential biomarkers for pediatric patients with AD.	China
Meng et al[59]	Journal of Proteome Research	4.4	Dermatopolimyositis	To provide a comprehensive description of proteome changes of plasma-derived exosomes in patients with DM/PM and indicate the clinical relevance of exosomal proteins as potential molecular markers for diagnosis and treatment of DM/PM.	China
Norooznezhad et al[30]	Heliyon	4.0	Alopecia	To report successful treatment of a patient suffering from PCIA with EVs derived from hUCMSCs.	NA
Oba et al[60]	J Immunol Res	4.1	AD	To perform a proteomic analysis with Th1- and Th2-derived EVs and identify HLA-DR as a Th1-dominated EV membrane protein.	NA
Ogawa-Momohara et al[61]	Journal of Investigative Dermatology	6.5	Cutaneous lupus	To understand if there is a disease-specific inflammation in CLE and SLE	NA
Okafor et al[62]	Arthritis and Rheumatology	13.3	SLE	To identify miRNA and other small RNA signatures that may be used as diagnostic biomarkers and potential therapeutic targets to limit either HMGB1- or TLR-induced inflammatory response in SLE.	NA

Ostergaard et al[63]	Journal of Extracellular Vesicles	16.0	SS	To characterize EVs from SS patients for comparison with EVs from HCs in the search for new disease biomarkers and improved understanding of disease mechanisms.	Denmark
Park et al[64]	J Cosmet Dermatol	2.3	AD	To investigate whether topical application of human adipose tissue-derived mesenchymal stem cell-derived exosomes could reduce dupilumab facial redness in patients with severe AD.	NA
Park et al[31]	J Cosmet Dermatol	2.3	Androgenic alopecia	To report the effects of exosomes from adipose-derived stem cells on hair loss	South Korea
Park et al[32]	J Cosmet Dermatol	2.3	Skin aging	To evaluate the clinical efficacy of combining the application of human ASCE-containing solution with microneedling to treat facial skin aging.	NA
Proffer et al[33]	Aesthet Surg J	3.1	Skin aging	To better characterize the safety and tolerability of novel human platelet extract intensive repair serum and its maximal effects on skin rejuvenation at 6 weeks.	USA
Pucci et al[65]	Journal of Extracellular Vesicles	16.0	SLE	To propose the isolation and purification of plasma EV from HC, SLE, and RA patients, comparing the vesicle profiles between them.	NA
Sasaki[34]	Aesthet Surg J Open Forum	3.1	Alopecia	To assess the safety, efficacy, and satisfaction of a single EV treatment over 6 months.	NA
Sawamura et al[73]	Journal of the European Academy of Dermatology and Venereology	9.2	Psoriasis	To investigate the levels of circulating emRNAs associated with the TNF/IL-23/IL-17 axis in the sera and its relevance as a potential biomarker in psoriasis.	NA
Shimada et al[66]	Journal of Dermatology	3.1	Psoriasis	To investigate circulating JAK2 emRNA levels to determine their clinical significance in psoriasis.	NA
Song et al[67]	HELIYON	4.0	SLE	To examine the rare expression profiles of circulating exosomal miRNAs and proteins in patients with SLE.	China
Sun et al[68]	Frontiers in Medicine	3.9	SS	To analyze potential biomarkers for SS by constructing lncRNA-miRNA-mRNA networks in cirexos.	China
Uto et al[69]	Rheumatology (Oxford)	5.5	Polymyositis, DM, SLE, and systemic scleroderma	To identify disease-specific surface proteins on EVs as novel serum biomarkers of PM/DM.	Japan

Continued

Table III. Cont'd

Author ID	Journal	Journal impact factor (2022)	Condition or disease approached	Objective	Country
Wang et al[70]	J Invest Dermatol	6.5	Psoriasis	To determine miRNA profiling of serum EVs in psoriasis	China
Wang et al[35]	Lasers Surg Med	2.4	Melasma	To explore the safety and efficacy of hUCMSC-Exos in the treatment of melasma and the means to promote its percutaneous penetration.	China
Yamaguchi et al[71]	Arthritis and Rheumatology	13.3	SLE	To extract urinal exosomes, detect miRNAs using nanowire devices, and identify biomarkers that could support SLE diagnosis and identify its status and severity.	NA
Yang et al[72]	Allergy Asthma Immunol Res	4.4	AD	To analyze the diversity and abundance of microbial EVs in sera collected from AD patients and HCs through 16S rDNA metagenomic analysis using NGS.	South Korea
Ye et al[36]	Front Bioeng Biotechnol	5.7	Skin sensitivity	To investigate the safety and efficacy of hUCMSC-Exos as a novel topical treatment for sensitive skin.	China
Zocco et al[77]	Scientific Reports	4.6	Melanoma	To investigate whether EV-associated DNA has value as an alternative source of circulating BRAFV600E.	Italy

AD, Atopic dermatitis; *ASCE*, adipose stem cell exosome; *BMMSC*, bone marrow mesenchymal stem cells; *BRAF*, mutation BRAF(V600E); *CaHa*, calcium hydroxylapatite; *CCC-ESF-1*, human embryonic skin fibroblast; *cirexo*, circulating exosomes; *CLE*, cutaneous lupus erythematosus; *CVU*, cardiovascular unit; *DM*, dermatomyositis; *DR*, disease resistance; *DRF*, dupilumab-related facial; *emRNA*, exosomal messenger RNA; *EV*, extracellular vesicle; *FCL*, fractional CO_2 laser; *HaCat*, human keratinocytes; *HC*, healthy control; *HLA-DR*, human leukocyte antigen-DR; *hUCMSC-Exos*, human umbilical cord mesenchymal stem cell-derived exosomes; *IL*, interleukin; *JAK2*, Janus kinase 2; *lncRNA*, long noncoding RNA; *mCRP*, monomeric C-reactive protein; *MK*, milk-derived exosome; *mRNA*, messenger RNA; *miRNA*, microRNA; *MK-Exo*, MK-derived exosomes; *MSC*, mesenchymal stem cell; *NGS*, next-generation sequencing; *PCIA*, persistent chemotherapy-induced alopecia; *pCRP*, pentameric C-reactive protein; *pEV*, platelet-derived extracellular vesicles; *PL*, *Phellinus linteus*; *PM*, polymyositis; *PsA*, psoriatic arthritis; *PsV*, psoriasis vulgaris; *RA*, rheumatoid arthritis; *rDNA*, ribosomal DNA; *s-EVs*, serum-, derived extracellular vesicles; *SLE*, systemic lupus erythematosus; *SS*, systemic sclerosis; *SV*, systemic vitiligo; *Th1*, type 1 T helper; *Th2*, type 2 T helper; *TLR*, toll-like receptor; *TNF*, tumor necrosis factor.
*2021.

Table IV. Additional characteristics of extracellular vesicles utilized among included studies based on their study design and settings

Study	EV type	Patient's characteristics	Study design	No. of patients	Assessment tool
Baniel et al[42]	Plasma-derived EVs	The study included patients diagnosed with DM (n = 21) without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	21	EV isolation, protein profile evaluated by LC-MS/MS, quantitative proteomics, and bioinformatics analysis of miRNAs.
Chang et al[43]	Plasma-derived exosomes	The study consisted of both healthy patients (n = 13) and patients diagnosed with AD (n = 12) based on the criteria of Williams et al[78] and according to the SCORAD index of at least 25 or higher patients (moderate-to-severe stages of disease). Among the healthy controls, the mean ± SD age was 43.23 ± 11.76 years, while in the AD group, the mean ± SD age was 52.33 ± 25.15 years.	Observational cross-sectional study and functional in vitro study	25	EV isolation, TEM for morphology evaluation, nano-flow cytometry for concentration and size distribution, WB for surface proteins quantification, LC-MS and MS analysis, and functional and STRING interaction network analysis
Chen et al[45]	Plasma-derived exosomal miRNA	The study included patients diagnosed with PV (n = 15), PsA (n = 30), RA (n = 15), and GA (n = 15) based on the Clinical Guidelines of Psoriasis 2008, EULAR 2010 Classification Criteria for RA, Classification Criteria for Psoriatic Arthritis, and ACR/EULAR 2015 Classification Criteria for GA, respectively. In addition, there were 15 healthy controls. Among the healthy controls, the mean ± SD age was 49.33 ± 8.15 years, while in the PV group, the mean ± SD age was 53.73 ± 14.88 years.	Observational cross-sectional study and functional in vitro study	90	Exosome isolation; SEM for morphology evaluation; nano-sight for size estimation; WB for surface proteins quantification; RNA extraction; small RNA library preparation; RT-PCR; cDNA sequencing; miRNAs profile evaluation; target gene prediction of commonly expressed miRNAs; bioinformatics analysis of miRNAs; potential miRNA target pairs and coexpression relationships assessment.
Chen et al[44]	Plasma-derived exosomal miRNA	The study included healthy (n = 15) and PV patients (n = 15). All selected PV patients fulfilled the Clinical Guidelines of Psoriasis 2008 formulated by the Chinese Medical Association. Among the mild healthy group, the mean ± SD age was 49.33 ± 8.15 years, while in the PV group, the mean ± SD age was 53.73 ± 14.88 years.	Observational cross-sectional study and functional in vitro study	30	Exosome isolation; SEM for morphology evaluation; nano-sight for size estimation; WB for surface proteins quantification; RNA extraction; small RNA library preparation; RT-PCR technique; RNA sequencing; microRNA levels and profiles analysis; target gene prediction; functional and STRING interaction network analysis.

Continued

Table IV. Cont'd

Study	EV type	Patient's characteristics	Study design	No. of patients	Assessment tool
Chernoff et al[21]	Placenta mesenchymal stem cell-derived EVs	The study included 35 females and 5 males, aged 34 to 72 years, without further specification of the patient's main characteristics.	Observational cohort study	40	Exosome isolation and purification, clinical photo documentation, and skin analysis according to Quantificare skin care score
Cho[22]	Human adipose mesenchymal stem cell-derived exosomes	The study included AD patients with DFR (n = 30) based on criteria not defined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	30	Skin evaluation based on average IGA and CEA scores, as well as evaluation of skin hydration and TEWL measures.
Cho[23]	Human adipose stem cell-derived exosome.	The study included 29 subjects treated with microneedling procedure and topical ASCE treatment (6 months) for facial skin aging based on criteria not defined by the study authors and without further specification of the patient's main characteristics.	Observational cohort study	29	Exosomes were isolated from serum-free conditioned media as recommended by the International Society for Extracellular Vesicles, and clinical assessment was performed according to the GAIS score.
Chouri et al[46]	Serum-derived exosomal miRNA	The study included SC patients (n = 26) with the extent of skin fibrosis as limited cutaneous or diffuse cutaneous SSc and healthy controls (n = 9) for miRNA profiling. Additional cohorts of 107 SSc patients and 24 healthy donors for miR-483-5p expression and validation set in serum of patients with localized scleroderma (n = 22), SLE (n = 33), and primary Sjogren's syndrome (n = 23) were also utilized.	Observational cross-sectional study and functional in vitro study	109	Blood analysis; RNA extraction; miRNA profiling; miRNA and gene expression analysis; exosome isolation; RNA extraction; functional in vitro assay; fibroblasts (primary dermal fibroblasts) and endothelial cell (human pulmonary artery endothelial cells) transfection with miR-483-5p and miR-483-5p, respectively.
Crescitelli et al[74]	Melanoma-tissue and blood-derived exosome	The study included 27 patients with a confirmed diagnosis of stage III or IV metastatic malignant melanoma based on criteria nondefined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	27	Isolation of EVs from HMC-1 cells, RNA extraction, and microarray analysis

Crescitelli et al[75]	Melanoma-tissue derived exosome	The study included 6 patients (4 males and 2 females) with stage III or IV melanoma based on criteria nondefined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	6	Protein concentrations of melanoma metastatic tissue-derived EVs evaluation; RNA isolation and purification; TEM analysis for morphology evaluation; WB for surface proteins quantification; nano-flow cytometry for concentration; size distribution, LC-MS and MS analysis; small RNA library construction; qRT-PCR analysis for miRNA.
Dong et al[47]	Serum-derived exosome	The study included 10 female SLE patients (mean ± SD, 26.9 ± 7.3 years) and 10 healthy female patients (mean ± SD, 27.2 ± 7.8 years). The diagnosis of all SLE patients was dependent on the criteria determined by the 2009 ACR.	Observational cross-sectional study and functional in vitro study	20	Extraction of exosomes from serum, TEM analysis for morphology evaluation, nano-sight for size estimation, NTA analysis, WB for surface proteins quantification, exosomal miRNA extraction, and qRT-PCR analysis
Doss et al[48]	Human skin-derived exosome	The study included patients with vitiligo (n = 50) and healthy controls (n = 50). Disease activity was estimated according to the VIDA score. Overall, 76% of patients were females and 24% were males. Patients' ages ranged from 18 to 65 years, with a mean ± SD of 27.24 ± 16.77. Overall, 30% of the control group were females, and 70% were males, and their ages ranged from 22 to 60 years, with a mean ± SD of 33.9 ± 9.35.	Observational cross-sectional study and functional in vitro study	100	Exosome isolation from skin biopsy, TEM analysis for morphology evaluation, exosomal RNA extraction and RT-PCR quantification, and-H19 and let-7a-5p obtention, and gene expression assays.
Gibello et al[24]	Serum-derived exosomes	The patients were eligible if they showed 2 or more distinct chronic lesions in the same limb. Chronic lesion was defined as the loss of skin tissue without any tendency to heal in the past 3 months. Four patients and 5 case-control lesions were enrolled in the study. The study population had a 77-year median age (IQR, 18), and 3 (75%) were females.	Case series	9	Immunopathological-related techniques (micron-thick paraffin sections, H&E, Masson's trichrome, and AFOG), immunochemistry-related assays, and histological assessments combined with digitalization scans.

Continued

Table IV. Cont'd

Study	EV type	Patient's characteristics	Study design	No. of patients	Assessment tool
Guo et al[49]	Plasma-derived exosome	The study included healthy donors (n = 48) and melanoma patients (n = 48) based on criteria not defined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	96	Exosome isolation; small RNA library construction, purification, and sequencing; qRT-PCR analysis for miRNA; in vitro analysis using human melanoma cell lines ME4405, A375, SK-Mel-5, Sk-Mel-28, and the human melanocyte cell line PIG1.
Han et al[25]	*Phellinus linteus* exosome-like nanovesicles	The study included 40 volunteers aged 20 to 35 years who participated in this experiment. The 40 volunteers were divided into 2 groups (n = 20): the control group (treated with basic cream) and the PL group (treated with cream containing 2% PL)	Observational cohort study	20	Clinical photo documentation, clinical assessment of skin erythema, skin hydration, TEWL, and biological analysis.
Han et al[26]	Human adipose mesenchymal stem cell-derived exosomes	The study included Korean patients (n = 20) aged 18 years and older who were on dupilumab for AD and were diagnosed with DFR based on criteria not defined by the study authors and without further specification of the patient's main characteristics.	Observational cohort study	20	Exosome extraction, purification, and characterization; exosome formulation into applicable formulation; size characterization with NTA analysis; clinical photo documentation; IGA score; CEA scale assessment; subjective satisfaction; assessment of skin erythema; skin hydration; TEWL.
Jacquin-Porretaz et al[50]	Circulating plasma exosomes	The study compared 2 groups of patients depending on psoriasis severity evaluated by BSA: patients with mild psoriasis (BSA $\leq$ 10%; n = 49) and patients with moderate-to-severe psoriasis (BSA $>$ 10%; n = 71). Among the mild psoriasis group, the mean $\pm$ SD age was 51.4 $\pm$ 14.2 years, while in the moderate-to-severe psoriasis group, the mean $\pm$ SD age was 47.8 $\pm$ 17.8 years.	Observational cross-sectional study and functional in vitro study	119	Exosome isolation and purification, WB for surface proteins quantification (TSG101, Alix, CD9, Syntenin-1, and HSP70), and flow cytometry for cytokines (IL-1-β, IL-2, IL-6, IL-10, IL-17A, and TNF-α)
Jang et al[76]	Isolation of EVs from melanoma metastases tissue	The study included healthy patients (n = 6) and patients with melanoma (n = 21), ovarian cancer (n = 62), and breast cancer (n = 13) who have disease stage III or IV based on criteria nondefined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	102	Exosome isolation, RNA extraction, and microarray analysis

Johnson et al[27]	Human platelet extracted exosomes	The study included healthy volunteers (n = 11) who were randomized and treated with clinical pEVs to one wound and with placebo to the comparator wound. Most participants were male (8/11, 72.7%) and white (10/11, 90.9%), with a mean age of 29.0 years.	Prospective, randomized, double-blind, placebo-controlled, single dose, single site clinical trial	11	LC-MS/MS analysis; pEV obtention and purification; fluorescence microscopy; cell migration assays; blood analysis; general biochemistry for metabolites and hormone measurements.
Karlsson et al[51]	Serum-derived EVs	The study included samples from patients classified with SLE (n = 67), based on the 1982 ACR and/or 2012 Systemic Lupus International Collaboration Clinics criteria, and a healthy group (n = 60). Among the SLE group, the mean ± SD age was 43 ± 12 years, while in the healthy group, the mean ± SD age was 43 ± 11 years.	Observational cohort study and functional analysis	127	Isolation of EVs from platelet-poor plasma (anticoagulated by citrate) and EV size by flow cytometry
Kwon et al[28]	Human adipose tissue stem cell-derived exosomes.	The study included 25 Korean subjects (18 men and 7 women; 12 with Fitzpatrick skin type III and 13 with type IV) with atrophic acne scars based on patients whose ECCA scores were 50 or higher. Among the ASCE group, the mean ± SD age was 35.6 ± 8.2 years (range, 19-54).	12-week prospective, double-blind, randomized, split-faced clinical trial	25	Exosome purification; exosome characterization by NT; clinical photo documentation; ECCA score; IGA score at each visit; subjective satisfaction.
Lättekivi et al[52]	Serum-derived EVs	The study included 2 distinct groups of patients, PsV (n = 12) and PsA (n = 12), and healthy controls (n = 12) based on criteria nondefined by the study authors. Each group consisted of 2 females and 10 males. The patients and controls were aged between 24 and 64 at the time of sampling, with the mean age of patients being 51 years.	Observational cross-sectional study and functional in vitro study	30	Exosome purification; TEM analysis for morphology evaluation; WB for surface proteins quantification; NTA analysis; proteomics assays; EVs array (multiplexed phenotyping); RNA extraction; qRT-PCR for RNA analysis; bioinformatics analysis of miRNAs.
Li et al[55]	Serum-derived EVs	SLE patients (n = 56) who were diagnosed for the first time and did not receive medication.	Observational cross-sectional study and functional in vitro study	56	Exosome purification; isolation of exosomes; RNA extraction; qRT-PCR for RNA analysis; bioinformatics analysis of miRNAs.

Continued

Table IV. Cont'd

Study	EV type	Patient's characteristics	Study design	No. of patients	Assessment tool
Li et al[53]	Serum-derived exosome	The study included patients with SV who had not received any treatment for at least 3 months (n = 30) and healthy volunteers (n = 30). Among the SV group, the mean ± SD age was 19.38 ± 10.29 years, while in the healthy group, the mean ± SD age was 17.93 ± 10.85 years.	Observational cross-sectional study and functional in vitro study	60	Exosome isolation; TEM analysis for morphology evaluation; WB for surface proteins quantification and NTA analysis; RNA extraction; qRT-PCR; high-throughput sequencing of exosomal miRNA for verification of differentially expressed miRNAs; primary cultures of normal human foreskin-derived keratinocytes and melanocytes.
Liu et al[54]	Serum-derived exosomes	The study included active vitiligo patients and healthy controls without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	NA	Exosome isolation, RNA extraction, and microarray analysis
Lu et al[29]	Bovine milk-derived exosomes	The study included female volunteers (n = 31) twice a day for 28 days without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	31	Exosome preparation; exosomal protein content; TEM analysis for morphology evaluation; WB for surface proteins quantification; nano FCM; proteomic analysis; LC-MS/MS analysis; differential miRNA enrichment analysis; in vitro assays for CCC-ESF-1 and HaCaT cell lines; MK-Exo uptake analysis; cell migration assays; safety evaluations for skin allergy; skin photoallergy; repeated skin irritation; skin photo-irritation tests; antiaging effect of MK-Exo in humans using the VISIA test (wrinkle assessment); skin hydration; skin elasticity.

Luo et al[56]	Human-derived serum exosome	The study consisted of both healthy individuals (n = 10) and patients with vitiligo (n = 10) diagnosed by Wood's lamp or reflectance laser confocal microscopy, and the VIDA score was ≥3. The vitiligo patients included 4 males and 6 females aged 18 to 72 years.	Observational cross-sectional study and functional in vitro study	20	Exosome isolation; RNA extraction; microarray analysis (miRNA library establishment and sequencing); diagnostic performance measures using the ROC curve and the lesions area correlation with miRNAs; target genes prediction of miRNAs; GO and KEGG analyses.
Maile et al[57]	Plasma-derived EVs	The study included burn patients (n = 50) admitted to the North Carolina Jaycee Burn Center without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	50	Exosome isolation; NTA analysis; flow cytometry analysis for detection and measurement of exosomes; proteomics assay; LC-MS/MS; EVs array (multiplexed phenotyping); RNA extraction; qRT-PCR for RNA analysis; target gene prediction evaluations.
Meng et al[58]	Pediatric Plasma Exosomes	The study included pediatric patients with AD (n = 23) meeting the Hanifin-Rajka diagnostic criteria and healthy controls (n = 23). The disease severity in patients was evaluated using the objective SCORAD index, according to which patients were divided into mild (range, 0-24 points), moderate (range, 25-50 points), and severe (range, 5-103 points) groups. Among the AD group, the mean age was 9.5 years (range, 3-13), while in the control group, the mean age was 9.0 years (range, 6-12).	Observational cross-sectional study and functional in vitro study	46	Exosome isolation, RNA extraction, and microarray analysis
Meng et al[59]	Plasma-Derived Exosomes	The study included DM (n = 17) patients and healthy controls (n = 9). All patients fulfilled the EULAR/ACR classification criteria for idiopathic inflammatory myopathies. Among the DM group, the mean ± SD age was 46.47 ± 13.54 years, while in the healthy group, the mean ± SD age was 42.11 ± 13.44 years.	Observational cross-sectional study and functional in vitro study	33	Exosome isolation; TEM analysis for morphology evaluation; WB for surface proteins quantification; NTA analysis; LC-MS assays; MS analysis; proteomics analysis (enrichment analysis for GO and KEGG pathways); PRM validation.

Continued

Table IV. Cont'd

Study	EV type	Patient's characteristics	Study design	No. of patients	Assessment tool
Norooznezhad et al[30]	Human placental mesenchymal stromal cell exosome-enriched EVs	The study included a 36-year-old woman with a history of invasive ductal carcinoma in the left breast, complaining of postchemotherapy hair loss followed by insufficient hair regrowth after the end of treatment despite waiting for 18 months.	Case report	1	Exosomes from human placenta mesenchymal stem cell isolation; TEM analysis for morphology evaluation; WB for surface proteins quantification; nano-sight for size determination; treatment: 3 sessions every 4 weeks for 18 months.
Oba et al[60]	Circulating plasma-derived exosomes, or EVs	The study included serum samples from patients with EBV infection, RA, or osteoarthritis without further specification of the patient's main characteristics. Patients with EBV infection were categorized into primary and recurrent infections based on the serum antibody pattern against EBV-related antigens. All RA patients were positive for the rheumatoid factor and anticyclic citrullinated peptide antibody test, and AD cases were diagnosed as ''moderate'' or ''severe'' by registered dermatologists.	Observational cross-sectional study and functional in vitro study	10	Purification and characterization of EVs; 2D-DIGE and MS; RNA extraction; microarray analysis.
Ogawa-Momohara et al[61]	Serum-derived exosomes	The study included healthy controls (n = 5), CLE patients (n = 6), and dermatomyositis patients (n = 17) based on criteria nondefined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	28	EV isolation; characterization by FACS and LC-MS/MS; RNA extraction; microarray analysis.
Okafor et al[62]	Plasma-derived exosomes	The study included 4 active female SLE patients meeting the revised criteria of the ACR and 3 age-/sex-matched healthy controls without further specification of the patient's main characteristics. Active disease was defined as a SLEDAI $>$ 4 at the time of sample collection.	Observational cohort study	7	Plasma-derived EV isolation, small RNA library preparation, and sequencing
Ostergaard et al[63]	Platelet-poor plasma exosomes	The study included healthy controls (n = 24) and patients diagnosed with SSc (n = 37) based on criteria nondefined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	61	Exosome isolation, RNA extraction, and microarray analysis

Park et al[64]	Human adipose stem cell-derived exosomes.	The study included 2 patients with AD (a 33-year-old man) and refractory DFR (a 28-year-old man) based on criteria nondefined by the study authors.	Case series	2	Exosome characterization; TEM analysis for morphology evaluation; WB for surface proteins quantification; FACS; clinical photo documentation; subjective satisfaction.
Park et al[31]	Adipose stem cell exosome	The study included patients (n = 39; 27 men and 12 women) with a mean age of 42.5 years (range, 20-66), based on criteria nondefined by the study authors.	Observational cohort study	39	Trichoscopy assessment (through Trichoscan)
Park et al[32]	Adipose tissue stem cell-derived exosomes.	The study included subjects with facial skin aging (n = 28) based on criteria nondefined by the study authors with a mean ± SD age of 54.0 ± 7.8 years.	Randomized clinical trial, 12-week, split-faced	28	Application of ASCE + Derma Signal Skin Rejuvenation Lyophilized Vial-S. Three treatment sessions every 3 weeks, followed up for 6 weeks after the last intervention. At each treatment session, HACS and microneedling were administered to one side of the face, and normal saline solution and microneedling to the other side as a control. Clinical photo documentation, GAIS at weeks 3, 6, and 12. Histopathological evaluations and instrumental evaluation.
Proffer et al[33]	Human platelet extract exosomes	The study included participants with Fitzpatrick skin types I to IV (n = 56), with mild to moderate global face wrinkles and moderate global fine lines based on modified Griffiths' 10-point scale. The mean ± SD age was 54 ± 11 years.	Observational cohort study	56	Topically applied platelet-derived exosome product; HPE; evaluation at baseline and 6 weeks; clinical photo documentation; white light and polarized imaging analyses.
Pucci et al[65]	Serum-derived exosomes	The study participants (n = 23) were assigned to 1 of 3 groups: G1, active SLE patients; G2, active RA patients; and G3, healthy control, based on criteria nondefined by the study authors and without further specification of the patient's main characteristics.	Observational cross-sectional study and functional in vitro study	23	Exosome isolation, RNA extraction, and microarray analysis

Continued

Table IV. Cont'd

Study	EV type	Patient's characteristics	Study design	No. of patients	Assessment tool
Sasaki[34]	Aseptic Human Bone Marrow Mesenchymal Stem Cell-Derived exosomes	The study included 9 males (average age, 43.3; range, 27-72 years) and 22 females (average age, 62.9; range, 28-80 years) based on male pattern hair loss grades III to IV based on the Norwood Hamilton Scale; female pattern hair loss with early limited or diffuse hair loss consistent with grades I-3 to III based on the Ludwig Scale; patients who experienced worsening responses or were in remission on minoxidil, finasteride, dutasteride, and spironolactone after a year on therapy and continued hair loss at least 6 months off medication(s); patients on supervised therapies consisting of estrogen/ progesterone/ testosterone/other pituitary replacement therapy or thyroid replacement therapy and experiencing hair thinning and loss on replacement therapies; who were treated with follicular unit extraction transplantation and experiencing hair thinning and loss in the transplanted and nontransplanted scalp a year after surgery.	Observational cohort study	31	EVs: XoFlo — EVs isolated from an aseptic human bone marrow mesenchymal stem cell, injected intradermally in the scalp, and evaluated after 6 months; BMI; clinical photo documentation; trichoscopic analyses; subjective satisfaction.
Sawamura et al[73]	Serum-derived exosomes	The study included 106 patients with psoriasis (77 patients with psoriasis vulgaris and 29 with psoriatic arthritis), and none of the patients were on systemic therapies during serum sampling based on criteria nondefined by the study authors and without further specification of the patient's main characteristic.	Observational cross-sectional study and functional in vitro study	106	NA
Shimada et al[66]	Serum-derived exosomes	The study included healthy controls (n = 28), patients with psoriasis vulgaris (n = 77), and patients with psoriatic arthritis (n = 29) based on criteria nondefined by the study authors and without further specification of the patient's main characteristic.	Observational cross-sectional study and functional in vitro study	134	Exosome isolation, RNA extraction, and microarray analysis

Song et al[67]	Plasma-derived exosomal miRNAs	The study included healthy controls (n = 20) and SLE patients (n = 10) based on SLE patients who were diagnosed with SLE disease and healthy patients who were not diagnosed with SLE or other immune diseases or treated with immunosuppressants. Among the SLE group, the mean ± SD age was 41.2 ± 15.23 years, while in the healthy group, the mean ± SD age was 37.80 ± 11.0 years.	Observational cross-sectional study and functional in vitro study	30	Exosome isolation and purification; TEM analysis for morphology evaluation; WB for surface proteins quantification; NTA analysis; exosomal RNA isolation and qualification; small RNA library construction and sequencing; bioinformatics analysis of miRNAs; proteomic assay; functional enrichment analysis of the GO and KEGG databases; prediction of miRNA-protein targeting pairs; verification of identified molecules in the exosome in plasma.
Sun et al[68]	Human blood-derived circulating exosomes	The study included 20 patients with SSc and 20 age- and sex-matched HCs without further specification of the patient's main characteristic. The inclusion criteria of patients with SSc were in accordance with the 2013 ACR/EULAR classification criteria.	Observational cross-sectional study and functional in vitro study	40	Extraction and identification of cirexos; TEM analysis for morphology evaluation; WB for surface proteins quantification; NTA analysis; high-throughput screening of DEmRNAs and DElncRNAs; analysis of GO and KEGG pathways; prediction of miRNAs targeted; prediction of lncRNA-miRNA-mRNA-ceRNA networks DElncRNAs and DEmRNAs; prediction of mRNA and lncRNA localization; prediction of upstream transcription factors and downstream binding proteins of lncRNAs; RT-PCR for ceRNA networks; correlation analysis between ceRNA networks and clinical data; ROC curve drawing.

Continued

Table IV. Cont'd

Study	EV type	Patient's characteristics	Study design	No. of patients	Assessment tool
Uto et al[69]	Serum-derived EVs	The study included patients with PM/DM (n = 54), RA (n = 24), SLE (n = 20), SSc (n = 13), DMD/BMD (n = 25), and healthy controls (n = 46)). Patients with PM/DM were diagnosed according to the definite or probable criteria of Bohan and Peter,[79] and patients with other autoimmune diseases met the established criteria for each disease. The mean ± SD age in the PM/DM group was 54.1 ± 15.7 years, while in the RA group, the mean ± SD age was 57.3 ± 11.3 years, in the SLE group 38.1 ± 16.9 years, in the SSc group 60.1 ± 9.2 years, in the DMD/BMD 14.4 ± 6.4 years, and in the healthy group 48.9 ± 7.2 years.	Observational cross-sectional study and functional in vitro study	709	Serum EV isolation; LC/MS followed by bioinformatics and biostatistical analyses to identify membrane proteins preferentially present in EVs of PM/DM patients; EV sandwich ELISA for detecting serum EVs expressing disease-specific membrane proteins.
Wang et al[70]	Serum-derived EVs	The study included patients with psoriasis (n = 52), patients with pityriasis rosea (n = 23), and healthy controls (n = 26) based on criteria nondefined by the study authors and without further specification of the patient's main characteristic.	Observational cross-sectional study, functional in vitro study, and validation assessment	101	Exosome isolation; RNA extraction; qRT-PCR for RNA analysis; miRNA target gene prediction.
Wang et al[35]	Human umbilical cord mesenchymal stem cell-derived exosomes	The study included 60 patients with melasma based on criteria nondefined by the study authors and without further specification of the patient's main characteristic.	Observational cohort study	60	Clinical photo documentation and clinical assessment evaluating the degree of pain posttreatment, melasma area and severity score, improvement rate, physician global assessment score, subjective satisfaction, and complications.
Yamaguchi et al[71]	Human-derived urinary exosomes	The study included SLE (n = 30) and non-SLE (n = 30) patients based on criteria nondefined by the study authors and without further specification of the patient's main characteristic.	Observational cross-sectional study and functional in vitro study	60	Exosome isolation, RNA extraction, and microarray analysis

Yang et al[72]	Serum microbial EVs	The study included AD patients (n = 24; 15 males and 9 females) and controls (n = 49; 35 males and 14 females). Children with moderate-to-severe AD diagnosed according to Hanifin and Rajka's[80] diagnostic criteria by pediatric allergy specialists were included in the study. The severity of AD was evaluated using the SCORAD index and disease duration (over 6 months). Healthy control subjects were screened through a general health examination. Among the AD group, the mean ± SD age was 10.5 ± 1.5 years, while in the control group, the mean age was 7.4 ± 5.3 years.	Observational cross-sectional study and functional in vitro study	73	Exosome isolation; DNA extraction; 16S rDNA metagenomic analysis using next-generation sequencing; analysis of bacterial composition in the microbiome
Ye et al[36]	Mesenchymal stem cell-derived exosomes	The study included healthy volunteers after informed consent (n = 22) aged 18 to 55 years whose 5% lactic acid stinging test scores were ≥3 and who had repeatedly dry, tingling, burning, itching, or other discomfort symptoms.	Observational cohort study	22	Exosomes from human umbilical cord mesenchymal stem cell isolation; TEM analysis for morphology evaluation; WB for surface proteins quantification; clinical assessment; subjective satisfaction.
Zocco et al[77]	Serum-derived exosomes	The study included patients with unresectable metastatic melanoma stage IIIC to IV (n = 50). All patients underwent tumor biopsy, which revealed that 20 of the patients' tumors (40%) were BRAFV600E-positive and 30 (60%) were BRAFWT-positive. There were 21 males and 29 females, with a median age of 67 years.	Observational cross-sectional study and functional in vitro study	50	Exosome isolation, RNA extraction, and microarray analysis

2D-DIGE, 2-Dimensional fluorescence difference gel electrophoresis; *ACR*, American College of Rheumatology; *AFOG*, Acid Fuchsin Orange G; *ASCE*, adipose stem cell exosome; *BMD*, Becker muscular dystrophy; *BMI*, body mass index; *BSA*, body surface area; *CCC-ESF-1*, human embryonic skin fibroblast-1; *cDNA*, complementary DNA; *CEA*, clinical erythema assessment scale; *ceRNA*, competing endogenous RNA; *Cirexos*, circular exosomes; *DEIncRNA*, differentially expressed lncRNA; *DEmRNA*, differentially expressed mRNA; *DFR*, Dupilumab facial redness; *DM*, dermatomyositis; *DMD*, Duchenne muscular dystrophy; *EBV*, Epstein-Barr virus; *ECCA*, *Échelle d'évaluation Clinique des Cicatrices d'Acné*; *ELISA*, enzyme-linked immunosorbent assay; *EULAR*, European League Against Rheumatism; *EV*, extracellular vesicle; *FACS*, fluorescence-activated cell sorting; *FCM*, flow cytometry measurement; *GA*, gouty arthritis; *GAIS*, Global Aesthetic Improvement Scale; *GO*, gene ontology; *HaCaT*, human keratinocytes; *HACS*, human ASCE-containing solution; *HC*, healthy controls; *H&E*, hematoxylin and eosin; *HMC-1*, human mast cell line-1; *HPE*, human platelet extract; *IGA*, Investigator's Global Assessment score; *IL*, interleukin; *KEGG*, Kyoto Encyclopaedia of Genes and Genomes; *LC-MS/MS*, liquid chromatography with tandem mass spectrometry; *lnc*, long noncoding; *lncRNA*, long noncoding RNA; *MK-Exo*, Bovine milk-derived exosomes; *mRNA*, messenger RNA; *miRNA*, microRNA; *NA*, not applicable; *NTA*, nanoparticle tracking analysis; *pEV*, plasma extracellular vesicles; *PL*, Phellinus linteus; *PM*, polymyositis; *PRM*, parallel reaction monitoring; *PsA*, psoriatic arthritis; *PV*, pemphigus vulgaris; *qRT-PCR*, reverse transcriptase quantitative polymerase chain reaction; *RA*, rheumatoid arthritis; *ROC*, receiver operating characteristic; *RT-PCR*, real-time-polymerase chain reaction; *SC*, stem cell; *SCORAD*, SCORing Atopic Dermatitis index; *SEM*, scanning electron microscopy; *SLEDAI*, Systemic Lupus Erythematosus Disease Activity Index; *SSc*, systemic sclerosis; *STRING*, Search Tool for the Retrieval of Interacting Genes; *SV*, systemic vitiligo; *TEM*, transmission electron microscopy; *TEWL*, trans-epidermal water loss; *TNF*, tumor necrosis factor; *VIDA*, vitiligo disease activity score; *VISIA*, standardized digital photographs to verify antiwrinkle effect; *WB*, Western blot.

Table V. Risk of bias and quality assessment of reporting of included studies

Study ID	Bias due to confounding	Bias in selection of participants for the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Observational cohorts appraised using the ROBINS-I methodology[38]								
Chernoff et al[21]	Critical	NI	Low	Low	Unclear	Critical	Low	Critical
Cho[23]	Critical	NI	Critical	NI	NI	Critical	NI	Critical
Han et al[25]	Critical	Serious	Moderate	Low	Low	Critical	Low	Critical
Han et al[26]	Critical	Serious	Low	Low	Low	Moderate	Low	Critical
Lu et al[29]	Critical	NI	Serious	Low	Low	Serious	Low	Critical
Okafor et al[62]	Critical	NI	NI	NI	Low	Moderate	Low	Critical
Park et al[31]	Low	Low	Moderate	NI	NI	Critical	Low	Critical
Proffer et al[33]	Low	NI	Low	Low	Low	Low	Low	Low
Sasaki[34]	Low	Serious	Low	Low	Low	Low	Low	Serious
Wang et al[35]	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Ye et al[36]	Low	Serious	Low	Low	Low	Critical	Low	Critical

Observational cross-sectional studies evaluated using an adapted version of the Newcastle-Ottawa Quality Assessment Scale as proposed by Zhao et al[82]

Study ID	Representativeness of the cases	Sample size	Nonresponse rate	Ascertainment of the screening/ surveillance tool	Investigation of confounders by subgroup analysis or multivariable analysis	Assessment of the outcome	Statistical test	Overall
Baniel et al[42]	0	0	0	1	0	2	1	4
Chang et al[43]	1	0	0	2	0	2	1	6
Chen et al[45]	1	0	0	2	0	2	1	6
Chen et al[44]	1	0	0	2	0	2	1	6
Chouri et al[46]	1	0	0	2	0	2	1	6
Crescitelli et al[74]	1	0	0	2	0	2	1	6
Crescitelli et al[75]	1	0	0	2	0	2	1	6
Dong et al[47]	1	0	0	2	0	2	1	6
Doss et al[48]	1	0	0	2	0	2	1	6
Guo et al[49]	1	0	0	2	0	2	1	6
Karlsson et al[51]	1	0	0	2	0	2	1	6
Jacquin-Porretaz et al[50]	1	0	0	2	0	2	1	6
Jang et al[76]	1	0	0	2	0	2	0	5
Lättekivi et al[52]	1	0	0	2	0	2	1	6
Li et al[55]	1	0	0	2	0	2	1	6
Li et al[53]	1	0	0	2	0	2	1	6
Liu et al[54]	0	0	0	1	0	2	0	3
Lu et al[29]	0	0	0	1	0	2	0	3

Maile et al[57]	1	0	0	2	0	2	1	6
Meng et al[58]	1	0	0	2	0	2	1	6
Meng et al[59]	1	0	0	2	0	2	1	6
Oba et al[60]	1	0	0	2	0	2	1	6
Ogawa-Momohara et al[61]	0	0	0	1	0	2	1	4
Ostergaard et al[63]	0	0	0	1	0	2	1	4
Pucci et al[65]	0	0	0	2	0	0	0	2
Sawamura et al[73]	0	0	0	0	0	0	0	0
Shimada et al[66]	0	0	0	2	0	2	0	4
Song et al[67]	1	0	0	2	0	2	1	6
Sun et al[68]	1	0	0	2	0	2	1	6
Uto et al[69]	1	0	0	2	0	2	1	6
Wang et al[70]	1	0	0	2	0	2	1	6
Yamaguchi et al[71]	0	0	0	0	0	0	0	0
Yang et al[72]	1	0	0	2	0	2	1	6
Zocco et al[77]	1	0	0	2	0	2	1	6

Quality reporting of case reports and case series using the Murad et al[39] approach

Study ID	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Domain 8
Cho[22]	Partially yes	Yes	Partially No	Yes	No	NA	Yes	No
Norooznezhad et al[30]	Yes	Yes	Yes	Yes	No	NA	Yes	Yes
Park et al[64]	Yes	Yes	Yes	Yes	No	NA	Yes	Yes

Risk of bias of randomized clinical trials using the Risk of Bias 2 tool by the Cochrane Collaboration[37]

	Randomization process	Deviation from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Cho[81]	Some concerns	Low	High	Low	Some concerns	High
Kwon et al[28]	Some concerns	Low	High	Low	Some concerns	High
Park et al[32]	Some concerns	Low	High	High	Some concerns	High

NI, No information.

label study among 22 female and 9 male patients reported increased terminal hairs, vellus hair counts, and follicle diameter, with average improvements ranging from 11% to 46% after they were given human bone marrow MSC-derived EVs subcutaneously on the scalp, particularly observed in the frontal-temporal region.[34] A cohort study including 29 patients reported an increase of 9 more hair counts per cm^2 after sessions of a microneedling procedure combined with topical allogenic adipose tissue MSC-EVs, implying improvement in clinical cases of androgenic alopecia and alopecia areata.[23] Lastly, Park et al[31] reported the findings from another cohort, suggesting statistically significant improvements with mean ± SD hair density increasing from 121.7 ± 37.2 to 146.6 ± 39.5 hairs per cm^2 ($P < .001$) and mean ± SD hair thickness increasing from 52.6 ± 10.4 to 61.4 ± 10.7 μm ($P < .001$) after topical adipose tissue MSC-derived EVs combined with microneedling protocols.

Acne scars. A double-blind, randomized, split-face trial utilized MSC-EVs applied topically after CO_2 laser treatment, which provided more rapid healing and reduced acne scarring.[28] Significant reductions in the "*Echelle d'Évaluation Clinique des Cicatrices d'Acné*" score were noted, with a 32.5% reduction observed versus placebo ([95% CI, 24.8%-40.2%] from baseline in the EV-treated arm vs a 19.9% reduction [95% CI, 12.2%-27.6%] with placebo [$P < .01$] at the final follow-up visit).[28] In addition, objective measurements using digital camera imaging showed reductions in the depressed volume of atrophic scars, the mean volume of skin pores, and skin surface roughness after EV treatment. The various treatment-related side effects that were reported, including posttreatment pain, erythema, edema, and dryness, in both groups were mostly mild and resolved within 5 days.[28]

AD. Three studies have evaluated the potential of EVs in AD.[22,26,64] Twenty AD patients with dupilumab-associated facial redness were included in a clinical trial where topical human adipose tissue MSC-EVs led to a significant improvement of disease severity scores in 85% of patients (score of 1 − "almost clear").[26] Similarly, Park et al[64] reported that 2 patients with AD and dupilumab-associated facial redness, not responding to standard treatment, did respond to topical MSC-derived EVs given with the support of electroporation. Data from a severe refractory AD case effect of autologous serum-derived EVs in a 28-year-old man who was given 6 sessions of treatment twice a week.[22]

Melasma. One study evaluated 60 treatments for melasma with topical human umbilical cord MSC-EVs or vehicle[35] and reported positive effects of EVs applied topically with or without concomitant microneedling.[35]

Wound healing. Two studies reported data on the use of EVs in wound healing.[24,27] A single dose of platelet-derived EVs was given subcutaneously after a skin punch biopsy-induced wound in 11 healthy volunteers. The study was prospective, randomized, double-blind, and placebo-controlled but failed to identify any difference in wound healing, whereas no adverse effects were observed.[27]

A single-center case-control study used autologous, "serum-derived EVs" in chronic venous ulcers, refractory to other interventions.[24] However, the isolation of EVs from serum is challenging, and other non-EV components in the isolates could have contributed to any observed improvements.[24]

Skin aging, skin rejuvenation, and skin sensitivity

Multiple studies have aimed to investigate the effects of EV-based products on skin rejuvenation and signs of skin aging.[21,25,29,32,33,36] Park et al[32] suggested that topical human adipose MSC-derived EVs, combined with microneedling, improve skin parameters (including texture, elasticity, and hydration) and reduce melanin levels (decreasing melanin index by 9.9%). Additionally, significant reductions in roughness indicators were observed, in parallel with increased skin elasticity.[32] Similarly, Han et al[25] suggested improvements in erythema index score, skin hydration parameters, and dermatologic changes that favor skin barrier reinforcement post-treatment with EV-like nanovesicles from a fungus (*Phellinus linteus*).

In a nonrandomized clinical trial, Proffer et al[33] reported reductions in fine lines, wrinkles, redness, and enhanced skin health scores following a 6-week protocol utilizing a daily topical human platelet extract of a leukocyte-depleted allogeneic product claimed to contain exosomes. The investigators observed decreased hemoglobin concentration and brown spots in photo-documented skin areas alongside increased skin luminosity and evenness.[33] Likewise, Lu et al[29] reported effects of topical bovine milk-derived EVs, indicating increased moisture content (4.64% on day 14 and 5.6% on day 28), brightness, and reduced wrinkle area (increase in the cutometer reading of F3/F4 and R2 by 6.33% and 7.24% on day 28, respectively). Additionally, Chernoff et al[21] demonstrated enhancement in skin quality, including skin tone evenness, clarity, reduction in fine lines, and improved texture (using automatic imaging protocols) after intradermal infusions of placenta MSC-derived EVs were combined with calcium hydroxyapatite. Another uncontrolled

study utilizing topical umbilical cord MSC-derived EVs for "sensitive skin" patients suggested beneficial effects on roughness, erythema, and subjective symptoms (ie, tension, burning sensation, or itching).[36]

The potential usefulness of EVs in the diagnosis and prognosis of the prioritized dermatologic diseases and conditions, including SLE,[47,51,55,62,65,67,69,71] scleroderma/systemic sclerosis,[46,63,68,69] dermatomyositis,[42,59,69] melanoma,[49,74-77] psoriasis,[44,45,50,52,66,70,73] vitiligo,[48,53,54,56] burn injury,[57] and AD,[22,26,43,58,60,64,72] are presented in the Supplementary Results (available via Mendeley at https://doi.org/10.17605/OSF.IO/ZY8K9).

DISCUSSION

Our review highlights the diverse utilization of EVs in dermatology, implying their potential roles across several dermatologic disorders. Some studies propose that EVs may be effective in treating multiple dermatologic diseases, although the level of evidence so far is low, with only a limited number of randomized studies published. The quality of the evidence is, therefore, considered weak due to methodologic inconsistencies, imprecision, and publication bias. Furthermore, EVs may also be useful as prognostic and diagnostic biomarkers in various diseases, including dermatologic ones, although again, the conclusiveness of current reports is weak.

Therapeutics role

This survey has identified reports of EVs in the clinical treatment of alopecia,[23,30,31,34] acne scar,[28] and AD,[22,26,64] although with overall low certainty of evidence, primarily because most studies are uncontrolled. In addition, EVs were reported to be effective in improving melasma[35] signs, also with low certainty of evidence. Additionally, benefits have been reported in wound healing, skin aging, and skin sensitivity.[21,25,29,32,33,36] Therefore, although the benefit of EVs has been observed in the treatment of these dermatologic conditions, conclusiveness is weak due to confounding factors, lack of controls, bias in classifying interventions, bias in measuring reported outcomes, imprecisions, small samples, and overall low-quality of objective reporting.[22,26,64]

Diagnostics and prognostics roles

EVs have also been widely evaluated and reported as diagnostic biomarker candidates for various dermatologic diseases. In comparison with healthy controls, serum-derived EVs from individuals with cutaneous diseases may have different phenotypes, for example, in SLE,[6,31,36,52,56,66,69,70] scleroderma,[46,63,68,69] psoriasis,[44,45,50,52,66,70,73] vitiligo,[48,53,54,56] skin tumors such as melanoma,[49,73,75-77] and burn injuries[57] (see Supplementary Results). Nevertheless, more comprehensive data are required for these biomarker candidates to allow for clinical translation. It is essential to identify biomarkers after appropriate EV isolation, characterization, and quantification.[83]

Plant-derived EV-like nanoparticles

Our study identified the lack of clinical studies utilizing EVs from nonhuman sources as therapeutics. Some recent evidence suggests that plant stem cell-derived or plant-derived EV-like nanoparticles may share some features with mammalian-derived EVs in terms of their structure and function.[84-87] Indeed, preclinical studies have suggested the effectiveness of plant- and fruit-derived EV-like nanoparticles in dermatology.[87-95] Topical formulations of *Rosa damascena* stem cell-derived EVs for cosmeceutical purposes have been recently released on the market globally as an anti-inflammatory and regenerative agent, with one in vitro study publicly available.[96,97]

Regulatory aspects

Concerning the regulatory aspects of using EVs as therapeutics, current legislation does not provide specific regulatory guidelines for EV-based therapies. Classification of EVs in a pharmaceutical category is challenging, considering the multifaceted functions and multiple sources of EVs that are being tested. Indeed, stem cell-derived EVs have been argued to be a "cell-free" cell therapy, entering the framework of the biologic medicinal products regulation under the definition of "biological medicine" (ie, a medicine that contains one or more active substances made by or derived from a biologic cell).[98] However, some EV-based therapies may share characteristics from both cell and gene therapies, which makes them complicated to classify in an existing pharmaceutic category.[99] In fact, EVs may also be considered an excipient or a device instead of an active substance when loaded with molecules and used as drug delivery systems.[100] Cosmeceutical EV-based products may, however, be different from pharmaceutic products, as the regulatory regime in this field is not as strict and differs widely in each country.[101] For that reason, injection of such products is strongly discouraged until safety has been well documented and injections have been approved from a regulatory perspective. Recently, the US Federal Food and Drug Administration officially clarified that some EV manufacturers claimed false and misleading therapeutic declarations about EV-derived products.[102,103] Most importantly, direct-to-consumer business marketing of

unproven or unlicensed EV-derived products should be strongly discouraged.[104]

Minimal requirements for EV studies and production

We observed that the assessed studies used EV-based products that were produced and characterized in a multitude of ways. Standardized methodologies for EV isolation, concentration, and characterization[105] should be applied for any clinical product and therapeutics; good manufacturing practices need to be followed in manufacturing.[106] Another important parameter is reproducibility and comparability of the results from different product batches, and clinical trials should be well designed and ideally double-blind and placebo-controlled.[107] In view of the numerous obstacles involving the study of EVs, the International Society of Extracellular Vesicles has recently published an updated guideline for the minimal requirements for research studies within the field of EVs, minimal information for studies of extracellular vesicles 2023.[108-111] This important attempt to standardize EV isolation and characterization guides not only laboratories and researchers but also contributes to physicians' critical sense of the available literature. For instance, in the cosmeceutical field, some products claim to contain EVs (exosomes), but this has often not been illustrated in any validated way. Further, in the United States, EVs from stem cells are injected into patients by some physicians for a variety of diseases without the approval of the US Federal Food and Drug Administration.[102,103] This is a major concern, as the safety and efficacy of any EV product should be documented in well designed and well performed controlled clinical trials, and the EVs must be manufactured in good manufacturing practice facilities.[112,113]

Study limitations

Despite the use of a solid and comprehensive methodology, our study has limitations that should be considered. First, most of the collated data originate from observational studies, which are affected by confounders and selection bias. Second, data from the primary studies were notably heterogeneous, which hinders the overall assessment of EVs using standard meta-analysis methodology. Third, some of the included studies were obtained from conference abstracts or conference proceedings, which also impacts the overall quality of data, including insufficiently detailed reporting, completeness, and transparency. Despite these limitations, we followed rigorous international guidelines for the execution of systematic reviews, including the utilization of a comprehensive search strategy. Further, we also adhered to predefined inclusion and exclusion criteria to minimize the risk of missing relevant studies and to ensure the evaluation of any bias among included studies.

CONCLUSIONS

EVs are being introduced into dermatology practices globally, including for cosmeceutical use. Observational studies have implied therapeutic efficacy, but from a regulatory perspective, no EV-based therapeutic has been approved. Future clinical studies of therapeutic EVs need to be randomized, double-blind and placebo-controlled to support regulatory approvals and objectivity. Likewise, diagnostic and prognostic findings need to be supported by data from large clinical cohorts before translation to clinical practice. Despite the long path to achieving regulatory approval of EV-based therapeutics, the already-existing information offers preliminary insights into the potential benefits of EVs for their medical translation in dermatology.

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

Conflicts of Interest

Declaration of Interest Statement

Taissa NovisTN, Adriano Henrique Gomes MenezesAHGM, Luan Cavalcante Vilaça LimaLCVL, Israel Júnior Borges do NascimentoIJBN, and Christina Maeda Takiya CMT have no competing interest or financial relationship with any pharmaceutical company. Israel Júnior Borges do Nascimento IJBN is an active Cochrane member. Jan Lötvall JL has equity in EV-focused startup biotechnology companies Exocure Sweden AB and Nexos Therapeutics AB (Sweden) and is a consultant for ExoCoBio Inc (South Korea). The author affiliated with the World Health Organization (Israel Júnior Borges do NascimentoIJBN) is alone responsible for the views expressed in this publication, and they do not necessarily represent the decisions or policies of the World Health Organization.

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