Supplementary Table 1 Application of exosomes secreted by other origins-derived stem cells in diabetic full-thickness acute cutaneous wounds model

No	Study (Year)	Institution (Nation)	Exosomes source	Intervention, administration, dose and time	Control	Model species	Wound diameter	Therapeutic effect	Molecular mechanism
1	Wang *et al.* (2021)[1]	The Second Affiliated Hospital of Harbin Medical University (China)	Human adipose tissue	1. HypADSC-Exos; injected subcutaneously into four mid-points of the wound edge; 2 mg in 100 μL PBS; at Day 0 2. ADSC-Exos; injected subcutaneously into four mid-points of the wound edge; 2 mg in 100 μL PBS; at Day 0	PBS (100 μl); Untreated	Nude mice (BALB/c)	0.8 cm × 0.8 cm (square)	1. Accelerated skin wound healing. 2. Complete re-epithelialization and cuticle covering on the epidermis. 3. Upregulated expression of collagens (Col I, Col III) and growth factors (CD31, TGF-β, PDGF, VEGF and PDGF); downregulated inflammatory factor (IL-6). 4. Improved angiogenesis (CD31, VEGF)	PI3K/AKT pathway
2	Shiekh *et al.* (2020	Indian Institute of Technolo	Rat adipose tissue	1. ADSC-Exos + PUAO-CPO scaffolds; applied on the wound beds; 100 μg/scaffold; at Day 0	Untreated	Rats (wister)	8 mm × 2	1. Accelerated wound closure. 2. Enhanced granulation tissue, epithelial, hair follicles and sebaceous glands formation, re-	— —

	)[2]	gy Kanpur (India)		2. ADSC-Exos + PUAO scaffolds; applied on the wound beds; 100 µg/scaffold; at Day 0 3. PUAO-CPO scaffolds; applied on the wound beds; 100 µg/scaffold; at Day 0 4. PUAO scaffolds; applied on the wound beds; 100 µg/scaffold; at Day 0				2. Increased fibroblast proliferation, collagen deposition (Col I, Col III) and remodeling (Col I remodeling). 4. Attenuated oxidative stress and increased angiogenesis. 5. Enhanced wound healing in *S. aureus* and *P. aeruginosa* infected diabetic wound ulcers	
3	Li *et al.* (2018)[3]	Tenth People's Hospital of Tongji University (China)	Rat and Human adipose tissue	1. Nrf2 overexpressed ADSC-Exos + EPCs; injected; dose not mentioned; at Day 0 2. ADSC-Exos + EPCs; injected; dose not mentioned; at Day 0 3. EPCs; injected;	PBS	Rats (Sprague-Dawley)	10 mm	1. Accelerated cutaneous wound healing. 2. Increased granulation tissue formation, angiogenesis, collagen deposition and the expression of growth factor. 3. Reduced levels of inflammation and oxidative stress (ROS)-related proteins.	— —

				dose not mentioned; at Day 0					
4	Wang *et al.* (2020)[4]	The Second Affiliated Hospital of Nanchang University (China)	Human adipose tissue	ADSC-Exos; injected into the dermis at the edge of the wound in 6 directions; 0.2 mL; at Day 0	PBS (0.2 mL)	Mice (BALB/c)	8 mm	1. Accelerated cutaneous wound healing. 2. Increased re-epithelization. 3. Promoted collagen synthesis and deposition (extensive deposited and neatly arranged collagen fibers). 4. Enhanced angiogenesis (CD31, number of microvessels).	——
5	Lv *et al.* (2020)[5]	The Third Affiliated Hospital of Sun Yat-sen University (China)	Human adipose tissue	1. miR-21-5p overexpressed ADSC-Exos; applied to the wound bed; 200 μL; at Day 0, every 3 days 2. ADSC-Exos; applied to the wound bed; 200 μL; at Day 0, every 3 days 3. ADSC-Exos (miR-21 negative control);	Untreated	Rats (Sprague-Dawley)	15 mm	1. Accelerated cutaneous wound healing. 2. Promoted collagen deposition, and tissue matrix remodeling. 3. Promoted re-epithelialization. 4. Controlled inflammation (limited inflammatory cells infiltrated). 5. Promoted angiogenesis and vascular maturation (CD31, α-SMA).	Wnt/β-catenin signaling pathway

				applied to the wound bed; 200 μL; at Day 0, every 3 days 4. miR-21-5p; applied to the wound bed; 200 μL; at Day 0, every 3 days					
6	Jiang *et al.* (2022)[6]	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (China)	Human adipose tissue	1. ADSC-Exos + matrix metalloproteinase degradable polyethylene glycol (MMP-PEG) hydrogel; dressed on the wound; dose not mentioned; at Day 0 2. MMP-PEG hydrogel; dressed on the wound; at Day 0	Traditional gauze	Mice (C57/BJ 6)	10 mm	1. Accelerated cutaneous wound healing. 2. Promoted re-epithelialization and collagen deposition. 3. Regrew cutaneous appendages. 4. Promoted cell mitosis (Ki67) and proliferation (PCNA) in diabetic wounds. 5. Enhanced angiogenesis (CD31, α-SMA). 6. Improved phosphorylation of AKT.	AKT pathway

7	Hsu *et al.* (2022)[7]	Chang Gung Memorial Hospital & Chang Gung University College of Medicine (Taiwan, China)	Diabetic mice adipose tissue	1. ADSC-Exos; topically treated; 200 μg in 200 μL PBS; at day 1, 4, 7, 10, 13 and 16 2. DFb-Exos; topically treated; 200 μg in 200 μL PBS; at day 1, 4, 7, 10, 13 and 16	PBS (200 μL)	Mice (db/db)	10 mm	1. Accelerated cutaneous wound healing. 2. Enhanced wound contraction and re-epithelialization. 3. Promoted granulation tissue formation and collagen deposition. 4. Increased proliferation (Ki67) of basal keratinocytes and dermal fibroblasts. 5. Promoted angiogenesis (CD31, α-SMA, VEGF). 6. Upregulated expression of stromal cell-derived factor (SDF)-1, keratinocyte growth factor (KGF). 7. Upregulate protein expression related to ECM remodeling (Col-I, α-SMA, Smad3 and TGF-β).	TGF-β/Smad3 signaling pathway
8	Qiu *et al.* (2021)[8]	The Second Xiangya Hospital	Human adipose tissue	1. linc00511 overexpressed ADSC-Exos + EPCs; injected; dose not mentioned;	PBS	Rats (Sprague-Dawley)	Not mentioned	1. Accelerated cutaneous wound healing. 2. Alleviated cutaneous tissue damages.	Suppressed PAQR3 enhanced

		of Central South University (China)	at Day 0 2. ADSC-Exos + EPCs; injected; dose not mentioned; at Day 0 3. EPCs; injected; dose not mentioned; at Day 0					3. Enhanced collagen deposition. 4. Promoted angiogenesis (CD31, VEGF) via inhibiting Twist1 protein degradation. 5. Suppressed inflammatory factors (IL-6, IL-1β, TNF-α). 6. Inhibited expression of PAQR3 and upregulated Twist1.	BTRC-mediated Twist1 ubiquitination and degradation.
9	Shi *et al.* (2022)[9]	Affiliated Hospital of Nantong University (China)	Adipose tissue	1. circ-Snhg11 overexpressed ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0 2. Hypoxia-pretreated ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0	PBS (100 μL)	Mice (db/db)	4 mm	1. Accelerated cutaneous wound healing (more effective). 2. Decreased expression of inflammatory factors (IL-6, IL-1β, TNF-α). 3. Promoted angiogenesis (CD34, VEGF). 4. Induced macrophage polarization from M1 (iNOS) to M2 (CD206) phenotype. 5. Increased STAT3 and VEGF expression.	circ-Snhg11/ miR-144–3p/HIF-1α/VEGF signaling pathway; circ-Snhg11/ miR-144–3p/HIF-1α/STAT

			Adipose tissue	1. Hypoxia-pretreated ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0 2. ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0	PBS (100 μL)	Mice (C57BL/6)	4 mm	1. Accelerated cutaneous wound healing. 2. Decreased expression of inflammatory factors (IL-6, IL-1β, TNF-α). 3. Promoted angiogenesis (CD34). 4. Induced macrophage polarization from M1 (iNOS) to M2 (CD206) phenotype. 5. Upregulated expression of circ-Snhg11.	3 signaling pathway
10	Liang *et al.* (2022)[10]	Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University) (China)	Mice adipose tissue	1. mmu_circ_0001052-modified ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL per sites; at Day 0 2. ADSC-Exos + vector; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL per sites; at Day 0	Untreated	Mice (BALB/c)	10 mm × 10 mm	1. Accelerated cutaneous wound healing. 2. Promoted angiogenesis (CD31). 3. Diminished inflammatory cells. 4. Promoted granulation tissue formation. 4. mmu_circ_0001052-modified ADSC-Exos promoted wound healing in DFU via miR-106a-	mmu_circ_0001052/miR-106a-5p/FGF4/p38MAPK pathway

								5p/FGF4/p38MAPK pathway (decreased miR-106a-5p and increased FGF4, VEGF, p-p38).	
11	Kobayashi *et al.* (2018)[11]	Nagoya University Graduate School of Medicine (Japan)	induced pluripotent stem (iPS) cell	1. iPS-Exos; injected subcutaneously; 4 μg in 20 μl PBS; at Day 0 2. M-Exos (isolated from unused iPS cell culture media); injected subcutaneously; 4 μg in 20 μl PBS; at Day 0	PBS (20 μl)	Mice C57BLKS/J-Leprdb (db/db)	8 mm × 2	1. Accelerated cutaneous wound healing. 2. Promoted re-epithelialization. 3. Enhanced angiogenesis (CD31, α-SMA, vessel density). 4. Promoted regeneration of peripheral nerve fibers (nerve density).	— —
12	Chen *et al.* (2018)[12]	Xiangya Hospital of Central South University (China)	Human urine	1. Con shRNA-transfected USC-Exos; injected subcutaneously around the wounds at 4 sites (25 μL per site); 200 μg in 100 μL PBS; at Day 0 2. DMBT1-silenced USC-Exos; injected subcutaneously around the wounds at 4 sites (25 μL per site); 200 μg in 100 μL PBS; at Day 0	PBS (100 μL)	Mice (C57BL/6)	6 mm × 2	1. Accelerated cutaneous wound healing. 2. Promoted re-epithelialization (longer newly formed epidermis and dermis with hair follicles and fat cells). 3. Reduced scar formation. 4. Promoted collagen deposition (larger amounts of wavy collagen fibers). 5. Enhanced proliferation of skin	DMBT1/VEGFA pathway; DMBT1/PI3K/AKT pathway

								cells in the wound sites (Ki67). 6. Enhanced angiogenesis (CD31, vessel density).	
13	Wang *et al.* (2022)[13]	Beth Israel Deaconess Medical Center of Harvard Medical School (USA)	Mice epidermal	1. Epidermal stem cell-derived exosomes (ESC-Exos); injected subcutaneous around the wound at 4 sites (40 µl per site) + at the wound center (40 µl); 50 µg/ml in total 200 µl PBS; at Day 0 2. Epidermal stem cells (ESCs); injected subcutaneous around the wound at 4 sites (40 µl per site) + at the wound center (40 µl); 5×10^6/ml in total 200 µl PBS; at Day 0 3. Fibroblast-derived exosomes (FB-Exos); injected subcutaneous around the wound at 4 sites (40 µl per site) + at the wound center (40 µl); dose not mentioned; at Day 0	PBS (200 µl)	Mice (db/db)	6 mm × 2	1. Accelerated cutaneous wound healing. 2. Promoted re-epithelialization (thicker epidermis). 3. Decreased wound inflammation (reduced inflammatory cells, NIMP-R14−positive neutrophils, F4/80positive Mfs, and degranulated mast cells). 4. Promoted wound cell proliferation (Ki67). 5. Enhanced angiogenesis (CD31, microvessel density, VEGF-A). 6. Elevated microcirculation and oxygen metabolism (tissue oxygen saturation). 7. Promoted macrophages polarization from M1 (iNOS, CD11b) to M2 (YM1, CD206,	TGF-β signaling pathway; PI3K/PKB pathway

								CD11b). Increased expression of CD31, PLGF-2, VEGF-A, and TGF-β3, prolactin, MMP-3, and TGF-β2.	
14	Ren *et al.* (2022)[14]	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (China)	Human adipose tissue	1. ADSC-Exos + normal mouse IgG; injected subcutaneous around the wound at 5 sites; 50ug ADSC-Exos; at Day 0 2. ADSC-Exos + normal mouse IgG; injected subcutaneous around the wound at 5 sites; 50ug ADSC-Exos; at Day 0 3. ADSC-Exos + anti-HSP90 antibody; injected subcutaneous around the wound at 5 sites; 50ug ADSC-Exos; at Day 0	PBS	Mice (C57BL/6)	9 mm	1. Accelerated cutaneous wound healing (anti-HSP90 antibody could completely inhibit this effect). 2. Promoted collagen deposition (more extensive and better-organized). 3. Alleviate oxidative stress (promoted ROS scavenging, reduced apoptotic cells). 4. Enhanced angiogenesis (CD31, α-SMA). 5. Promoted cell proliferation in granulation tissue (Ki67, PCNA).	exosomal HSP90/LRP1/AKT signaling pathway

References

1 **Wang J**, Wu H, Peng Y, Zhao Y, Qin Y, Zhang Y, Xiao Z. Hypoxia adipose stem cell-derived exosomes promote high-quality healing of diabetic wound involves activation of PI3K/Akt pathways. *J Nanobiotechnology* 2021; **19**: 202 [PMID: 34233694 DOI: 10.1186/s12951-021-00942-0]

2 **Shiekh PA**, Singh A, Kumar A. Exosome laden oxygen releasing antioxidant and antibacterial cryogel wound dressing OxOBand alleviate diabetic and infectious wound healing. *Biomaterials* 2020; **249**: 120020 [PMID: 32305816 DOI: 10.1016/j.biomaterials.2020.120020]

3 **Li X**, Xie X, Lian W, Shi R, Han S, Zhang H, Lu L, Li M. Exosomes from adipose-derived stem cells overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model. *Exp Mol Med* 2018; **50**: 1-14 [PMID: 29651102 DOI: 10.1038/s12276-018-0058-5]

4 **Wang J**, Yi Y, Zhu Y, Wang Z, Wu S, Zhang J, Hu X, Nie J. [Effects of adipose-derived stem cell released exosomes on wound healing in diabetic mice]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2020; **34**: 124-131 [PMID: 31939247 DOI: 10.7507/1002-1892.201903058]

5 **Lv Q**, Deng J, Chen Y, Wang Y, Liu B, Liu J. Engineered Human Adipose Stem-Cell-Derived Exosomes Loaded with miR-21-5p to Promote Diabetic Cutaneous Wound Healing. *Mol Pharm* 2020; **17**: 1723-1733 [PMID: 32233440 DOI: 10.1021/acs.molpharmaceut.0c00177]

6 **Jiang T**, Liu S, Wu Z, Li Q, Ren S, Chen J, Xu X, Wang C, Lu C, Yang X, Chen Z. ADSC-exo@MMP-PEG smart hydrogel promotes diabetic wound healing by optimizing cellular functions and relieving oxidative stress. *Mater Today Bio* 2022; **16**: 100365 [PMID: 35967739 DOI: 10.1016/j.mtbio.2022.100365]

7 **Hsu HH**, Wang AYL, Loh CYY, Pai AA, Kao HK. Therapeutic Potential of Exosomes Derived from Diabetic Adipose Stem Cells in Cutaneous Wound Healing of *db/db* Mice. *Pharmaceutics* 2022; **14** [PMID: 35745779 DOI: 10.3390/pharmaceutics14061206]

8 **Qiu J**, Shu C, Li X, Ye C, Zhang WC. Exosomes from linc00511-overexpressing ADSCs accelerates angiogenesis in diabetic foot ulcers healing by suppressing PAQR3-induced Twist1 degradation. *Diabetes Res Clin Pract* 2021; **180**: 109032 [PMID: 34461141 DOI: 10.1016/j.diabres.2021.109032]

9 **Shi R**, Jin Y, Zhao S, Yuan H, Shi J, Zhao H. Hypoxic ADSC-derived exosomes enhance wound healing in diabetic mice via delivery of circ-Snhg11 and induction of M2-like macrophage polarization. *Biomed Pharmacother* 2022; **153**: 113463 [PMID: 36076572 DOI: 10.1016/j.biopha.2022.113463]

10 **Liang ZH**, Pan NF, Lin SS, Qiu ZY, Liang P, Wang J, Zhang Z, Pan YC. Exosomes from mmu_circ_0001052-modified adipose-derived stem cells promote angiogenesis of DFU via miR-

106a-5p and FGF4/p38MAPK pathway. *Stem Cell Res Ther* 2022; **13**: 336 [PMID: 35870977 DOI: 10.1186/s13287-022-03015-7]

11 **Kobayashi H**, Ebisawa K, Kambe M, Kasai T, Suga H, Nakamura K, Narita Y, Ogata A, Kamei Y. < Editors' Choice > Effects of exosomes derived from the induced pluripotent stem cells on skin wound healing. *Nagoya J Med Sci* 2018; **80**: 141-153 [PMID: 29915432 DOI: 10.18999/nagjms.80.2.141]

12 **Chen CY**, Rao SS, Ren L, Hu XK, Tan YJ, Hu Y, Luo J, Liu YW, Yin H, Huang J, Cao J, Wang ZX, Liu ZZ, Liu HM, Tang SY, Xu R, Xie H. Exosomal DMBT1 from human urine-derived stem cells facilitates diabetic wound repair by promoting angiogenesis. *Theranostics* 2018; **8**: 1607-1623 [PMID: 29556344 DOI: 10.7150/thno.22958]

13 **Wang P**, Theocharidis G, Vlachos IS, Kounas K, Lobao A, Shu B, Wu B, Xie J, Hu Z, Qi S, Tang B, Zhu J, Veves A. Exosomes Derived from Epidermal Stem Cells Improve Diabetic Wound Healing. *J Invest Dermatol* 2022; **142**: 2508-2517.e13 [PMID: 35181300 DOI: 10.1016/j.jid.2022.01.030]

14 **Ren S**, Chen J, Guo J, Liu Y, Xiong H, Jing B, Yang X, Li G, Kang Y, Wang C, Xu X, Liu Z, Zhang M, Xiang K, Li C, Li Q, Machens HG, Chen Z. Exosomes from Adipose Stem Cells Promote Diabetic Wound Healing through the eHSP90/LRP1/AKT Axis. *Cells* 2022; **11** [PMID: 36291096 DOI: 10.3390/cells11203229]