MLTJ
Muscles, Ligaments and Tendons Journal

REVIEW

EFFICACY AND SAFETY OF EXOSOMES AND EXTRACELLULAR VESICLES IN THE MANAGEMENT OF ROTATOR CUFF INJURY: A SYSTEMATIC REVIEW OF IN VIVO STUDIES

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Received: 15/09/2025
Accepted: 06/11/2025
Published: 31/03/2026

Conflict of interests: The Authors declare that there are no competing interests.
Fundings: This research did not receive any fundings grant from funding agencies in public, commercial, or not-for-profit sectors.
Data availability: All data generated or analyzed during this study are derived from previously published articles indexed in PubMed, Scopus, Wiley as described in the Methods section.
Contributions: WKS, AA, SIC, RKA were responsible for conceptualization, search strategy, and study design for this review. WKS, SIC, RKA, PA did all database searching. WKS, SIC, RKA, DKL, KGS, and PA did the article screening and data extraction. Any disagreements during the screening process were resolved collectively by all authors. WKS was responsible for data curation, while WKS, DKL, KGS, RKA contributed to data analysis and data interpretation. All authors contributed to reviewing and editing the final manuscript.
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LEVEL OF EVIDENCE: 2b

ABSTRACT

Introduction: Rotator cuff tendon is vulnerable to acute and chronic injuries, leading to pain, reduced mobility, and decreased quality of life. Recovery is slow and frequently results in fibrotic changes, impairing full functional restoration. Currently, exosomes and extracellular-vesicles (EVs) have emerged as promising regenerative approaches for tendon. However, no clinical studies in humans have been reported for its use in rotator cuff injury. Therefore, this review aims to evaluate the efficacy and safety of exosomes/EVs in animal models of rotator cuff injury, as a foundation for clinical translation.

Methods: A systematic search was conducted following PRISMA guidelines across PubMed, Scopus, Wiley, and EBSCOhost. Eligible studies included animal models of rotator cuff injury treated with exosomes/EVs. Data on exosomes/EVs characteristics, animal model, outcomes, and follow-up duration were extracted. Risk of bias was assessed using SYRCLE RoB tool.

Results: Eleven studies were included in the review, involving 63 mice, 210 rats, 211 rabbits, and 12 sheep. Variations were noted in sources, concentration, and delivery methods for exosomes/EVs across studies. Exosomes/EVs demonstrated superior outcomes in tendon repair compared to controls, with improvements observed in macroscopic, histological, and biomechanical outcomes. Proposed mechanisms included enhanced extracellular matrix remodeling, reduced fatty infiltration, anti-inflammatory, and immune-modulation. Quality of included studies was generally moderate, with some studies exhibiting some risk of bias.

Conclusion: Exosome and EVs might be effective for rotator cuff injury in animal models with minimum side effects. Further preclinical studies and clinical trials are necessary to validate efficacy and safety in humans.

KEYWORDS

Exosomes, extracellular vesicles, rotator cuff injuries, tendon repair, in vivo

Publisher
smc media srl

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INTRODUCTION

The shoulder's stability is maintained by a group of muscles and tendons known as the rotator cuff, which plays a critical role in stabilizing the glenohumeral joint[1]. The anatomical configuration of this joint prioritizes mobility over stability, making it particularly susceptible to injuries[1]. Injury to the rotator cuff is common, particularly in occupations involving repetitive overhead movements, such as heavy manual labor, or as a result of shoulder dislocations[1]. In younger individuals, rotator cuff injury commonly results from trauma, while in the elderly, degenerative tears are more prevalent[1]. Approximately 20% of the general population has a rotator cuff injury and 48.4% of them are asymptomatic, suggesting a high probability of underreported or undiagnosed cases[2]. This prevalence increases with age, with individuals over 60 years having a two-fold higher risk[2].

Rotator cuff injuries often result in pain and limited mobility, leading to significant loss of productivity[1]. Due to the lack of regeneration capacity, healing of tendons tends to be slow and often result in fibrosis, limiting full functional recovery[1,3,4]. Recently, surgical techniques such as arthroscopic approaches have become the standard method for rotator cuff repair due to a smaller incision, less invasive, reduced need for muscle dissection, and less post-operative pain[5]. Although these procedures have a reported success rate of up to 90%, they still carry a risk of failure and re-tear cases, largely due to inadequate regeneration at the bone-tendon-insertion (BTI)[4,5]. Currently, no established regenerative therapies are available to promote rotator cuff repair[6]. This situation is similar to cartilage repair, where few effective therapies have been found due to its low regenerative capacity[7]. Considering the high burden and limitations of current treatments, it is crucial to assess new therapies that could regenerate the tendon and improve outcomes[4].

In recent years, cell-free therapy derived from mesenchymal stem cells (MSCs) has emerged as a promising treatment approach for tendon injuries. Cell-free therapy, particularly exosomes and extracellular vesicles (EVs), in several cases, are preferred over stem cell-based approaches due to their less-immunogenic nature, less toxicity, easier to access and preserve, and free from tumorigenic potential or ethical concerns[8,9]. Compared to MSCs, MSC-derived exosomes (MSC-exos) have the advantage of avoiding phagocytic clearance and remaining in circulation for extended periods[10]. Several in vitro and in vivo studies have explored the potential of exosomes and EVs regarding their application in rotator cuff injury[8]. However, practical use of exosomes is restricted by the limited secretion capability of cells[11], which poses a challenge for large-scale clinical application. To date, there are still no studies in clinical settings despite the promising evidence from preclinical studies[12]. Therefore, this review aims to systematically evaluate the efficacy and safety of exosomes and EVs in animal models of acute and chronic rotator cuff injury, therefore, adding literature as a foundation for further trials in humans.

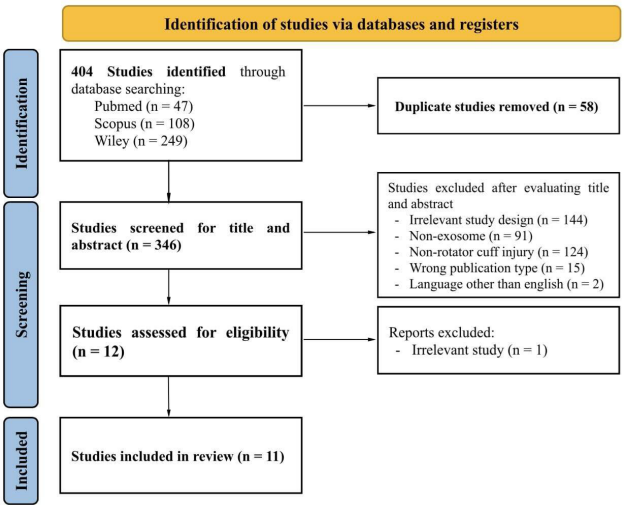


Figure 1. *PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart for literature search strategies[13].*

METHODS

Search criteria and screening

This review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251069432)[13]. A literature search was performed across PubMed, Scopus, and Wiley using the following keywords, either individually or in combination: tendon, rotator cuff, exosome, extracellular vesicle, heal, repair, and regeneration (See Appendix N). Studies investigating the use of EVs or exosomes in vivo as a therapeutic intervention for acute and chronic rotator cuff injury with outcomes related to tendon healing were included. Studies were excluded if they were in silico/in vitro, non-original research (e.g., reviews, letters, conference abstracts, book chapters, or editorial), duplicates, or published in a language other than English.

Data extraction

Seven independent and blinded reviewers (WKA, AA, SIC, RKA, DKL, PA, KGS) conducted screening for abstract and title using Rayyan QCRI Software. Following initial screening, full texts were assessed to identify studies meeting eligible criteria. In case of a difference in study selection, the reviewers discussed the matter until an agreement was reached. From each included study, descriptive data was collected, including: (1) Intervention details (exosomes/EVs type, cell origin, delivery method); (2) Animal model characteristics (type, number, age, weight, gender, and preparation); (3) Experimental group; (4) Outcome (macroscopic, histological, and biomechanical); (4) Follow up duration; and (5) Suggested mechanisms of action. Screening and data extraction were completed in May 2025.

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	Selection bias			Performance bias		Detection bias		Attrition bias	Selective outcome reporting	Other source of bias	
Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Overall
He et al., 2024[16]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Zhang et al., 2024[17]	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Low
Wang et al., 2020[18]	Low	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear
Zhang et al., 2024[14]	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Cai et al., 2023[15]	Low	High	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Jenner et al., 2023[19]	Low	Low	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Low
Tong et al., 2023[20]	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low
Ren et al., 2021[21]	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low
Kim et al., 2022[22]	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low
Zhang et al., 2022[23]	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Tan et al., 2024[24]	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low

Figure 2. *Quality assessment of included studies using SYRCLE risk of bias tool[15].*

Macroscopic outcomes such as tendon continuity, signs of infection or rejection, and the extent of fibrotic tissue formation were extracted from each paper. Histological outcome, evaluated through semiquantitative histological scoring systems assessing vascularity, cellularity, and collagen fiber characteristics (orientation, continuity, and density) were also included in our analysis[14]. Lastly, to assess the functional outcome, biomechanical assessments such as maximal failure load and stiffness, as well as gait analysis parameters including average pressure intensity, footprint area, and swing time were extracted. Extracted data was synthesized as a qualitative summary, using a narrative approach, for each study.

Risk of Bias Assessment

The Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) tool was used to assess potential biases in the included in vivo studies[15], Seven blinded reviewers (WKA, AA, SIC, RKA, DKL, PA, KGS) independently evaluated risks of bias in the included studies. Any difference of opinion was solved in discussion with the team. Confidence in the body of evidence for each outcome was discussed narratively, considering study design, consistency of findings, and directness of evidence.

RESULTS

Search Results

After searching through 3 databases, 404 studies were gathered. Following the elimination of duplicates, 346 studies undergo screening for title and abstract. During initial screening, 334 studies were excluded due to inappropriate study design (n=144), not using exosomes or EVs as treatment (n=91), conditions other than rotator cuff injury (n=124), wrong publication type (review or editorials) (n=15), and studies not published in English (n=2). Following full-text screening, eleven studies met the inclusion criteria and were included in the review for further data extraction and risk of bias assessment, while one study was excluded due to an incorrect study design.

Assessment of Quality of Studies

To assess the quality of each study, we leveraged The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias assessment tool to evaluate the selection bias, performance bias, detection bias, attribution bias, reporting bias, and other biases in the studies[15]. All of the studies are deemed to have an overall low risk of bias (54,5%), and the rest (45,4%) are unclear.

The allocation sequence of each animal model was randomized adequately, with some studies mentioning the methods of the allocation process. Most of the studies had a balanced distribution of animal models with similar baseline characteristics in both control and the intervention groups. However, two studies had an imbalance and unclear group distribution system[16,17]. Moreover, none of the studies referred to the randomized housing condition of the animals, and the information regarding caregivers/investigators who were blinded to the intervention given during the experiment.

Although the outcome assessors were reported to be blinded in most studies, the randomization for outcome assessment was unclear. Most of the studies reported all

Author & Year	Exosome/ EV type	Delivery Method	Animal model					Animal preparation/ Mechanism of injury	Type of Rotator Cuff Injury
			Type	Number	Age	Weight	Gender		
He et al., 2024[16]	TSPC-Exos Col@PDA TSC-exos-S	Suturing the TSC-exos-S at the torn tendon end and fixed at the anatomic footprint through bone tunnel (dose: 3x10^11).	Rats	10	10 weeks	N/A	Male	Retraction of the supraspinatus tendon at the insertion on the greater tuberosity of the humerus. Animals were evaluated at week 4 and week 8.	Acute rotator cuff injury
Zhang et al., 2024[17]	TSC-Exos-S (TSC-Exos and COL-I into PCL-S)	Suturing the TSC-exos-S between the distal edge of the torn supraspinatus tendon and the decorticated greater tubercle.	Rabbits	48	16 weeks	2.5 kg	Male	Creation of a 5-mm longitudinal supraspinatus tendon defect at the insertion on the greater tubercle following exposure through shoulder incision and deltoid retraction. After 12 weeks, the tendon was re-exposed and released from fibrotic adhesions by blunt dissection.	Chronic UMRCT
Wang et al., 2020[18]	ADSC-Exos	Injection of 10^11 ASC-Exos in 20 mL saline per site at the distal site of supraspinatus muscle.	Rabbits	35	16 weeks	3.3 ± 0.3 kg	Male	Detachment of the supraspinatus tendon at the insertion on the greater tuberosity of the humerus and wrapping with a silicone Penrose drain to prevent adhesion. At week 6, rabbits were evaluated for outcome assessment.	Chronic rotator cuff tear
Zhang et al., 2024[14]	S-TSC-Exos Me-Ha H-TSC-Exos-HA	Intraperitoneal injection of Me-Ha and h-TSC-Exos-HA (liposomal clodronate (1.33 ml/100 g).	Rats	78	15 months	N/A	Male	Detachment of the infraspinatus tendons from the footprint on the greater tubercle creates a full-thickness injury, leaving it unrepaired for 12 weeks with layered soft-tissue closure.	Chronic rotator cuff tear
Cai et al., 2023[15]	un-Exos KGN-Exos	Injection of exosome loaded into SAH scaffold.	Rats	66	12 weeks	270–310 g	Male	Sharp bilateral resection of the supraspinatus on both shoulders of each rat from the greater tuberosity of the humeral head. The presence of DiR/DiI-labeled exosomes was assessed at 1 day and 1 week, and tendon-to-bone healing was evaluated at 4 and 8 weeks.	Chronic rotator cuff tear
Jenner et al., 2023[19]	HUC-MSC-sEVs loaded into COL-I scaffold	Local application of EVs loaded onto collagen sponge.	Sheep	12	2-4 years; (median 3.5 years)	67–99 kg (median 84 kg)	Female	Partial infraspinatus tenotomy creating a 7-mm full-thickness defect using punch biopsy and calipers with enthesis debridement. 6 weeks post-operation, the healing of the tendon was evaluated.	Acute rotator cuff injury
Tong et al., 2023[20]	CD133$^+$ USC-Exos	Application of Exosome + Adhesive Hydrogel (dose: 100 μg), In situ UV-crosslinked adhesive hydrogel.	Rats	20	N/A	300–350 g	Male	Separation of the supraspinatus tendon and reattachment to the humerus. Animals were evaluated at week 4 and week 8.	Acute rotator cuff injury
Ren et al., 2021[21]	PEP	Application of TISSEEL fibrin scaffold-embedded PEP exosomes directly onto the supraspinatus tendon-bone footprint following rotator cuff surgical repair.	Rats	36	6 weeks	258–552 g	Female	Surgical detachment and transosseous repair of the supraspinatus tendon to the humeral footprint. 6 weeks after surgery, animals were evaluated.	Acute rotator cuff injury
Kim et al, 2022[22]	EVs derived from HUC-MSCs	Administration of EVs mixture with collagen to injured rotator cuff.	Rabbits	20	12 weeks	2.83 ± 0.36 kg	Male	Induction of chronic cuff tear by wrapping the tendon stump with a Silastic drain to prevent self-healing and retraction of the supraspinatus tendon to the glenoid side. 6 weeks after the creation of tear, chronicity of the BTI was examined	Chronic rotator cuff tear model
Zhang et al., 2022[23]	MSC–Exos	MSC-Exos-loaded patch fixed to the proximal of supraspinatus muscle using two interrupted sutures.	Rabbits	108	16 weeks	2.5 kg	Male	Complete transection of the supraspinatus tendon from the greater tubercle via a 1-cm incision under sterile conditions. The torn tendon was left unrepaired for 12 weeks to establish a chronic tear model.	Chronic rotator cuff injury
Tan et al., 2024[24]	ADSC-Exos BMSC-Exos	Local injection of 20μg of exosomes between the tendon and tuberosity with a 30-gauge insulin syringe.	Mice	63	6 - 8 weeks	N/A	Male	Surgical detachment of the supraspinatus tendon from the greater tuberosity, removal of the fibrocartilage layer, and reattachment via bone tunnel using sutures with postoperative free movement for 4 or 8 weeks.	Acute rotator cuff injury

Table 1. *Summary of Study Characteristics and Animal Model Used.*

Abbreviations: ADSC-Exos, Adipose stem cell- derived exosome; BMSC-Exos, bone marrow-derived mesenchymal stromal cells; BTI, Bone-Tendon Interface; CD133$^+$ USC-Exos, CD133$^+$ human urine-derived stem cells; Col@PDA, Collagen@Polydopamine; ECM, Extracellular Matrix; FL, Fascia Lata; HUC-MSC, human umbilical cord mesenchymal stem cells; hUC-MSC-sEVs, Human umbilical cord MSC-derived Small extracellular vesicles; KGN-Exos, exosomes derived from mesenchymal stem cells preconditioned with kartogenin; Me-Ha, Methacrylated Hyaluronic Acid; MSC–Exos, mesenchymal stem cells-derived exosomes; PEP, Purified Exosome Product (PEP); RCE, Repair + Collagen + Exosomes; REPA, Repair + Exosome-loaded Patch Augmentation; SAH, Exosome-loaded sodium alginate hydrogel; TSC-Exos-HA, TSC-Exos Hyaluronic Acid; TSC-Exos-S, TSC-Exos scaffolds; UMRCT, Unrepairable massive rotator cuff tears; un-Exos, Unprocessed exosomes.

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outcome data, with only one study showing incomplete reporting due to the death of an animal model caused by issues unrelated to the given treatment[18]. All studies were deemed as free from selective outcome reporting and free from issues that might raise the potential for bias. Therefore, the included studies demonstrated a generally low or unclear risk of bias, with the main concerns centered around the lack of clarity in randomization concealment, housing conditions, and blinding of personnel involved in the experiments.

Study Characteristics

Types of Exosomes or Extracellular Vesicles

We noticed a heterogeneity in the sources of exosomes or EVs and the use of additional scaffolds in the included studies *(Table 1)*. Most of the exosomes utilized are retrieved from human stem cells such as human bone marrow mesenchymal stem cells (hBMSCs)[17], human umbilical cord mesenchymal stem cells (hUC-MSCs)[19], $CD133^+$ human urine-derived stem cells (USCs)[20], and purified exosome product (PEP) from human blood cells[21]. Two studies used MSCs-derived exosomes from rabbits and mice (ASC-Exos and BMSC-Exos)[22,23]. Three studies used tendon stem cells (TSC) that are taken mainly from rats and rabbits[16,24,25]. Additionally, one study employed small extracellular vesicles (sEV) derived from hUC-MSCs[18].

Delivery Methods

The predominant method of delivering the exosomes or EVs is by local delivery at the injury or repair site[19,23,26] and scaffolds[16–18,21,24], while two studies utilized hydrogel[20] and patch[22]. Several studies applied exosomes embedded in biomaterials such as collagen scaffolds, TISSEEL fibrin glue, sodium alginate hydrogels, or fiber-aligned patches that were sutured or placed directly onto the defect injury site[18,21,24,25]. Other studies used direct injection methods, for instance, ASC-Exos in saline injected near the supraspinatus muscle[26], Exosome-loaded alginate hydrogel injection[17], weekly exosomes injection with an insulin syringe between the tendon and tuberosity[23], and injection of Methacrylated-Hyaluronic Acid (Me-Ha) and H-TSC-Exos-HA on the injured infraspinatus tendon[16]. Overall, localised scaffold-based delivery is the most preferred method of all the studies.

Animal Models

Among the included studies, rats and rabbits were the most frequently used models. Other studies utilized sheep[18] and mice[23]. The mechanism of injury to induce rotator cuff tears varied across the studies, both to induce acute[18,20,21,23,24] or chronic injuries[16,17,19,22,25,26]. Injury is considered acute when the duration is less than 4 weeks after injury, while it is classified as chronic if it persists more than >4 weeks[27]. In most studies, a full-thickness detachment of the supraspinatus tendon from its insertion at the greater tuberosity of the humerus was performed to mimic the typical site of rotator cuff injury[16,17,22,23,25,26]. This procedure was frequently followed by surgical repair, often combined with different scaffolds or exosomes. Several studies incorporated specific procedural adjustments to enhance the chronicity and severity of the injury, such as performing bilateral tendon defect[17,25] and application of silicone drain around tendon to prevent natural healing, thus inducing a chronic injury[19,26]. Most studies perform follow-up for 4 to 18 weeks post-operation.

In vivo study outcomes

The included studies consistently demonstrate that exosomes and EVs significantly improve rotator cuff repair outcomes, both in acute and chronic injury *(Table 2)*[16–26]. Macroscopic observations in several studies reported intact tendon continuity and the presence of abundant, fibrous-like, and well-integrated regenerated tissue at the repair site[22,25]. Some also noted increased bone regeneration at the insertion site (BTI)[24] and significantly reduced fibrotic adhesion to surrounding tissue[18]. No studies reported signs of infection, immune rejection, or retear.

Biomechanical analyses showed better healing in groups treated with exosomes or EVs, with significantly higher ultimate load to failure, greater stiffness, and increased stress to failure compared to control[16,17,19–21,23–26]. Some studies performed gait analysis, which results in larger footprint area[24] and enhanced total work to failure[20], indicating stronger BTI healing and improved biomechanical strength[17,20].

Exosomes and EVs treatment resulted in higher histological scores in multiple studies[17,19,20,24–26], indicating enhanced tendon regeneration and maturation[20]. Groups receiving exosomes or EVs also demonstrated fewer inflammatory cells[21,24] and reduced fatty infiltration in the supraspinatus muscle[19,22,25,26], as well as prevention of fibrous scar-like tissue formation[20,25]. Other parameters such as regeneration of BTI, collagen I deposition and organization, and fibrocartilage formation were also higher in exosomes or EVs group[19,21,22,24–26].

Majority of studies used a semiquantitative scoring system[17,20–22,25,26] with a few studies having other scoring systems such as Watkins scores[18], histomorphometric score[19], and quantitative score[16]. Notably, two studies did not demonstrate clearly its scoring system[23,24]. Histomorphometric score in a study was used because it is considered more subjective and semiquantitative compared to histomorphometric scoring to assess the BTI regeneration[19].

DISCUSSION

Exosomes and EVs have been proposed as a treatment option for tendon injuries to address challenges resulting from current treatments, particularly limited tendon regeneration, retear, and failure in achieving maximum functionality. In this review, we found that

Author	Macroscopic appearance	Biomechanical analysis	Histology	Suggested mechanisms
He et al., 2024[16]	Increased tendon regeneration at the insertion site in the Col@PDA & T-Exos group (p<0.05)	Higher ultimate load to failure and greater stiffness, and greater gait in Col@PDA&T-Exos group (p<0.05)	Fewer inflammatory cells, better collagen organization and morphology, higher collagen type I expression, and higher histological score in Col@PDA&T-Exos group (p < 0.01 at 4 weeks; p < 0.001 at 8 weeks)	TSPC-Exos enhance the proliferation, migration, and fibrogenic differentiation of BMSCs; Suppression of inflammation by inhibition of M1 macrophage polarization; Promoted regeneration, enhancing functional and structural aspects of tendon-bone healing.
Zhang et al., 2024[17]	Abundant fibrous-like regenerated tissue with well-integration at the greater tubercle in all groups and absence of infection, immune rejection, or retears	Highest ultimate load to failure and greater stiffness in the TSC-Exos-S compared to control and other experimental groups (p<0.05)	Most organized tendon-like tissue, highest type I collagen expression, strongest bone integration, and improved histological score in the TSC-Exos-S (p < 0.001 at 8 weeks; p < 0.001 at 16 weeks) and FL groups (p < 0.001 at both time points)	Enhanced tendon matrix regeneration by increasing and organizing collagen I deposition; reduced fatty infiltration and fibrous scar formation; immunomodulation
Wang et al., 2020[18]	Visible extra-muscular fat on supraspinatus muscle surface after surgery in all groups; no post-intervention description reported	Higher ultimate load to failure and greater stiffness in the ASC-Exos group compared to saline (p<0.05)	Lower fatty infiltration, increased fibrocartilage, collagen II, tenascin-C, collagen I deposition and organization, and improved histological score in the ASC-Exos group (p < 0.05)	Prevention of fatty infiltration; promotion of fibrocartilage formation
Zhang et al., 2024[14]	More abundant fibrous tissue with better arrangement in the h-TSC-Exo-HA group compared to Control and Me-HA groups	Higher ultimate load and stress to failure in the h-TSC-Exo-HA group compared to control and Me-HA groups (p<0.05)	More organized fibrous tissues and better arrangement in the h-TSC-Exo-HA group with improved histological score at all time points (p < 0.001)	Skewing macrophage polarization from M1 to M2 phenotype in the h-TSC-Exo-HA group
[20]al et al., 2023[15]	N/A	Higher ultimate failure load and stiffness at 4 and 8 weeks in the KGN-Exos and un-Exos groups than in controls; highest in the KGN-Exos group (p<0.05)	Improved histological score (p < 0.05), largest cartilage metachromasia area, highest collagen II expression, and highest collagen ratio after 1 and 3 months in the KGN-Exos group	Exosome-mediated effect on local or recruited cells; immunomodulation; cartilage formation and collagen organization in the KGN-Exos group
Jenner et al., 2023[19]	Coverage of all defects with fibrotic tissue and significant reduction of fibrotic adhesion in the sEV-treated group; absence of residual collagen sponges	N/A	Better tendon repair and tendon–bone insertion, reduced osteophyte formation in the sEV-treated group, and improved Watkins scores (p = 0.031)	Reduction of inflammation and apoptosis; increased cell proliferation and ECM remodeling; shift of inflammatory balance toward regeneration; suppression of osteophyte formation
Tong et al., 2023	N/A	Highest failure load, stiffness, and total work to failure at 8 weeks in the CD133⁺ USC-Exos group compared to USC-Exos and control groups (p<0.05)	Most organized fibrocartilage structure, clearer tendon–bone interface, more mature enthesis formation, and highest histological maturation score at 4 and 8 weeks in the CD133⁺ USC-Exos group (p < 0.05; p < 0.01)	Promotion of fibrocartilage regeneration; prevention of fatty infiltration and fibrous scar formation; activation of Wnt/β-catenin pathway; enhancement of osteogenic and chondrogenic differentiation of BMSCs
Ren et al., 2021[21]	N/A	Highest ultimate failure load and stiffness at 6 weeks in the TISSEEL-PEP compared to other experimental groups (p<0.05)	More organized and dense collagen fibers, fewer inflammatory cells, tendon–bone interface resembling native enthesis in the TISSEEL-PEP group, and improved histological scores (p < 0.05)	Enhanced collagen matrix remodeling; stimulation of tenogenic differentiation; promotion of cell migration and interface fusion; reduction of inflammation and scarring
Kim et al., 2022[22]	Well-organized BTI structure with clear tidemark and aligned collagen in normal specimens; increased fatty degeneration in supraspinatus muscle in the chronic tear model (8.5% vs. 0.8%)	Greater load-to-failure and stiffness in the collagen + hUC-MSC-EVs group compared to collagen-only and controls (p<0.05)	More mature and organized BTI, thicker fibrocartilage, higher collagen type I alignment, and greater histomorphometric score (p < .001, and P = 0.013 for RCE group	Collagen mixed with EVs synergistic effect during bone-tendon insertion maturation; protection against fatty degeneration in the RCE group
Zhang et al., 2022[23]	Intact tendon continuity without infection or retears; augmentation patch encapsulated by fibrous tissue and no longer distinguishable	Higher ultimate failure load and stiffness at 8 and 12 weeks in the REPA group compared to surgical only or RFPA group (p<0.05)	Better tendon-to-bone integration, increased collagen deposition, organized structure, fibrocartilage formation, reduced fatty infiltration in the REPA group, and improved histological score (p<0.05) for RFPA and REPA groups	Reduction of fatty infiltration; anti-inflammatory effect repressing infiltration of lipid-laden macrophages that may differentiate into adipocytes in the REPA group
Tan et al., 2024[24]	Better bone quality around injury surface at postoperative 4 and 8 weeks in the ADSC-Exos and BMSC-Exos groups shown by Xradia radiographic evaluation	Greater mechanical strength at 4 and 8 weeks in the ADSC-Exos and BMSC-Exos groups than in controls; no significant difference between exosome groups	Organized fibrovascular tissue at bone-tendon insertion by 4 weeks; enhanced BMSC proliferation and migration in the ADSC-Exos and BMSC-Exos groups, both outperforming controls; improved histological score (p < 0.05)	Promotion of BMSC proliferation, migration, and differentiation into osteoblasts and chondroblasts; augmentation of new bone formation and fibrocartilage regeneration; improvement of BTI organization in the ADSC-Exos and BMSC-Exos groups

Table 2. *Summary of in vivo study results.*

Abbreviations: ADSC-Exos, Adipose stem cell- derived exosome; BMSC-Exos, bone marrow-derived mesenchymal stromal cells; BTI, Bone-Tendon Interface; CD133⁺ USC-Exos, CD133⁺ human urine-derived stem cells; Col@PDA, Collagen@Polydopamine; ECM, Extracellular Matrix; FL, Fascia Lata; HUC-MSC, human umbilical cord mesenchymal stem cells; hUC-MSC-sEVs, Human umbilical cord MSC-derived Small extracellular vesicles; KGN-Exos, exosomes derived from mesenchymal stem cells preconditioned with kartogenin; Me-Ha, Methacrylated Hyaluronic Acid; MSC–Exos, mesenchymal stem cells-derived exosomes; RCE, Repair + Collagen + Exosomes; REPA, Repair + Exosome-loaded Patch Augmentation; RFPA, repaired with fiber-aligned patch augmentation; SAH, Exosome-loaded sodium alginate hydrogel; TSC-Exos-HA, TSC-Exos Hyaluronic Acid; TSC-Exos-S, TSC-Exos scaffolds; PEP, Purified Exosome Product (PEP); un-Exos, Unprocessed exosomes.

exosomes and EVs significantly enhance tendon healing in preclinical models of rotator cuff injury, both in acute and chronic cases. Most of the included studies showed marked improvements in biomechanical strength, histological structure, and BTI following exosomes or EVs treatments[16–26].

The pathophysiology of tendon healing involves a complex cascade. In acute cases, there is a leakage of synovial fluid, disruption of local blood supply, and infiltration of inflammatory cells[28]. Whereas, chronic injuries are characterized by chronic inflammation, fibrovascular scarring, and fatty infiltration, leading to incomplete BTI healing[26,28,29]. Following injury, immune cells, particularly macrophages, infiltrate the affected area within the first 48 hours, initiating collagen synthesis over 3 weeks. The final regeneration phase will start months after, involving collagen I deposition, maturation and reorganization. However, the regenerated tissue often exhibits scarring with inferior biomechanical properties compared to native tendon[28]. This tendinopathy phenomenon might be linked to prolonged inflammation, resulting from sustained cytokine secretion at the injury site. Supporting this notion, Giancola, et al., 2022 reported an increased CD200 expression as a potential mediator of the inflammatory response during tendon injury[30].

Exosomes and EVs have shown potential in addressing tendon's pathological cascades by modulating inflammatory environments, enhancing the intrinsic regenerative capacities of tendon, and promoting collagen organization[31–35]. Exosomes and EVs promote polarization of macrophages into anti-inflammatory M2 phenotype, which helps to resolve chronic inflammation as seen in studies utilizing TSPC-Exos[24], ASC-Exos[26], and hUC-MSC-sEVs[18]. At the cellular level, exosomes and EVs facilitate proliferation, migration, and differentiation of stem cells and tendon progenitor cells, which further accelerate the inner tendon healing[20,21,24,34,35]. This was also evident in the administration of EVs derived from rat bone-marrow MSCs for Achilles tendon injury, resulting in an accelerated tenocytes proliferation and migration, as well as increased expression of collagen 1 and MMP14 as a marker of tendon remodeling[35]. Additionally, they might improve mechanical strength by increasing type I and II collagen deposition and organization at the repair site[25,35]. This was align with a study from Gissi et al., which demonstrated a better organization of tendon-fiber alignment in achilles tendon injury model following administration of EVs derived from BM-MSCs[35].

Certain exosome subtypes used in the included study, including $CD133^{+}$ USC-derived exosomes and kartogenin-preconditioned BM-MSC-derived exosomes, have been shown to upregulate SOX9, a transcription factor essential for chondrogenesis[20]. Moreover, exosomes have been reported to suppress adipogenic pathways through miR-21a-5p[24], reducing fatty infiltration that might impair tendon regeneration and promote fibrosis. miR-21-a-5p is also involved in enhancing mechanical strength after tendon injury by activating PDCD4/AKT/mTOR pathway, which induce proliferation, migration, and fibrogenesis of inner stem cells in tendon[24].

Although positive results were seen in most studies, determining the most effective type of exosomes/EVs remains challenging. Heterogeneity in the type of exosomes or EVs used, dosage, delivery methods, additional treatment, as well as study design make it difficult to draw conclusions. However, we noticed that exosomes and EVs incorporated into scaffolds such as hydrogels are often outperformed exosomes alone, likely due to sustained release, prolonged local retention, and enhanced cellular responses[17,20,21,24]. Scaffolds loaded exosomes also increased expression of COL-I in tendon, resulting in improved mechanical strengths compared to exosomes only[25]. Similar findings have been observed in other cases, such as non-union bone fracture, where the combination of scaffolds (e.g. hydroxyapatite) and MSCs products significantly enhanced bone regeneration[9]. This effect is likely due to improved MSCs retention within the scaffold and the ability of the scaffold to provide a more favorable microenvironment that supports MSC viability, function, and paracrine signaling[9]. In line with this, conditioned medium from umbilical cord-derived MSCs has been shown to increase IGF-1 production, which can inhibit pro-apoptotic pathways (e.g., BAX) and maintain growth differentiation factor 9 (GDF9) expression[36], illustrating how paracrine factors can directly influence cellular survival and regenerative capacity in target tissues.

Hyaluronic acid (HA), used in several included studies, is frequently used in tissue engineering due to its compatibility and biodegradability nature[37]. HA might serve as an effective carrier to encapsulate growth factors, cells, and bioactive molecules that are easily inactivated, thus prolonging the activity of encapsulated drugs[37]. Additionally, HA might enhance vascularization and transform the proinflammatory environment to anti-inflammatory, such as switching the macrophage into M2 type at the BTI, leading to better healing results[16,37].

Several studies have applied preconditioning strategies to MSCs to boost their therapeutic potential and exosomes content, for example by exposing them to proinflammatory mediators (e.g.IFN-γ, TNF-α, IL-1α, IL-1β, IL-17a)[34,38], herbal compounds (e.g. lycium, icariin, and Cissus quadrangularis)[39–42], hypoxic condition[43], or other compounds[44]. Among these, herbal-derived agents have garnered attention due to their ability to promote osteogenic and chrondrogenic diferentiation of MSCs. For instance, one of the included studies performed preconditioning of BM-MSCs with kartogenin, and its exosomes showed improved cartilage formation as well as collagen synthesis, maturation, and organization[17]. This is likely due to the dual ability of kartogenin to stimulate both tenogenic and chondrogenic differentiation, as demonstrated by Zhu et al. (2019)[45]. Moreover, exosomes

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derived from kartogenin-preconditioned BM-MSCs might overcome the limitation of kartogenin alone, which are less water-soluble and have low effective concentration[17].

Regarding safety, none of the included studies reported adverse effects following exosomes/EVs treatment. This might be due to the nature of exosomes/EVs that pose less immunogenicity than live stem cell transplants, lower possibility of immune rejection, and less potential of tumor formation[20,21].

However, we noted some limitations in the included studies. First, the differences in anatomy, biomechanics, and immune responses between animal models and humans limit the generalizability of the findings[46,47]. Second, the methodological heterogeneity, including variations in exosomes types, dosages, delivery methods (direct injection, scaffolds, hydrogels), and types of animal model, limits the ability to draw definitive conclusions regarding the effectiveness and proposed mechanisms of exosomes in rotator cuff injury. Third, short follow-up duration might limit our understanding of the long-term efficacy and durability of exosomes, particularly in prevention of retear over time. Fourth, there is a potential risk of bias related to randomization and blinding, as most studies did not provide detailed reporting on group allocation processes, random housing, or blinding of caregivers and investigators. However, these aspects are often inadequately addressed in animal studies[48]. Finally, although results in animal models appear promising; to date, no clinical trials have been conducted in humans[12]. Therefore, further research is needed to evaluate the safety, optimal dosing, mechanisms of action, and clinical effectiveness of exosomes therapy before it can be widely implemented in humans.

Future studies should include longer follow-up periods to assess the long-term efficacy and safety of exosome therapy. Standardized outcome measurements, including macroscopic appearance, biomechanical testing, and histological scoring (e.g. Bonar or Movin scores), are recommended to improve comparability. Proper randomization, housing, and blinding should also be implemented to reduce bias, with comprehensive toxicity and immunogenicity evaluations before human application. Moreover, employing larger animal models such as rabbits, canines, sheep, or goats is needed to better replicate human conditions, as these models provide more reliable assessments of functional outcomes, including biomechanical performance, compared to smaller rodents like mice or rats. Furthermore, clinical trials in humans should be initiated as pilot projects to evaluate preliminary safety and efficacy data.

CONCLUSION

Exosomes and extracellular vesicles derived from various sources might be efficacious and safe for acute and chronic rotator cuff injury in animal models.

REFERENCES

1. May T, Garmel GM. Rotator Cuff Injury. Treasure Island (FL): StatPearls [Internet]. 2025 [cited 2025 May 31]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547664/
2. Hinsley H, Ganderton C, Arden NK, Carr AJ. Prevalence of rotator cuff tendon tears and symptoms in a Chingford general population cohort, and the resultant impact on UK health services: a cross-sectional observational study. BMJ Open. 2022;12:e059175. doi: 10.1136/bmjopen-2021-059175.
3. Darrieutort-Laffite C, Blanchard F, Soslowsky LJ, Le Goff B. Biology and physiology of tendon healing. Joint Bone Spine. 2024;91(5):105696. doi: 10.1016/j.jbspin.2024.105696.
4. Johnson J, Gadomski B, Regan D, Johnson J, Nelson B, McGilvray K, et al. Biomechanical enhancement in rotator cuff repairs: the impact of innovative nanofiber technology. JSES Int. 2025;9:116–22. doi: 10.1016/j.jseint.2024.08.203.
5. Pierami R, Antonioli E, Castro IQ, Fairbanks P, Manente FG, Lenza M. Clinical outcomes and direct cost analysis of rotator cuff repair surgery. Einstein (Sao Paulo). 2024;22:eGS0473. doi: 10.31744/einstein_journal/2024GS0473.
6. Kim J, Ryu Y, Kim SH. Surgical Options for Failed Rotator Cuff Repair, except Arthroplasty: Review of Current Methods. Clin Shoulder Elb. 2020;23(1):48–58. doi: 10.5397/cise.2019.00416.
7. Amsar RM, Wijaya CH, Ana ID, Hidajah AC, Notobroto HB, Kencana Wungu TD, et al. Extracellular vesicles: a promising cell-free therapy for cartilage repair. Future Sci OA. 2022;8(2):FSO774. doi: 10.2144/fsoa-2021-0096.
8. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. Signal Transduct Target Ther. 2024;12;9(1):17. doi: 10.1038/s41392-023-01704-0.
9. Kamal AF, Dilogo IH, Hutagalung EU, Iskandriati D, Susworo R, Siregar NC, et al. Transplantation of mesenchymal stem cells, recombinant human BMP-2, and their combination in accelerating the union after osteotomy and in-creasing, the mechanical strength of extracorporeally irradiated femoral autograft in rat models. Med J Islam Repub Iran. 2014;28:129.
10. Xue Y, Riva N, Zhao L, Shieh JS, Chin YT, Gatt A, et al. Recent advances of exosomes in soft tissue injuries in sports medicine: A critical review on biological and biomaterial applications. J Control Release. 2023;364:90–108. doi: 10.1016/j.jconrel.2023.10.031.
11. Ana ID, Barlian A, Hidajah AC, Wijaya CH, Notobroto HB, Kencana Wungu TD. Challenges and strategy in treatment with exosomes for cell-free-based tissue engineering in dentistry. Future Sci OA. 2021;7:FSO751. doi: 10.2144/fsoa-2021-0050.
12. Kuhn JE. Prevalence, Natural History, and Nonoperative Treatment of Rotator Cuff Disease. Oper Tech Sports Med. 2023;31:150978. doi: 10.1016/j.otsm.2023.150978.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.
14. Chatterjee M, Evans MK, Bell R, Nguyen PK, Kamalitdinov TB, Korntner S, et al. Histological and immunohistochemical guide to tendon tissue. J Orthop Res. 2023;41:2114–22. doi: 10.1002/jor.25645.
15. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43. doi: 10.1186/1471-2288-14-43.
16. Zhang X, Song W, Liu Y, et al. Healthy tendon stem cell-derived exosomes promote tendon-to-bone healing of aged chronic rotator cuff tears by breaking the positive-feedback cross-talk between senescent tendon stem cells and macrophages through the modulation of macrophage polarization. Small. 2024;20(31):e2311033. doi: 10.1002/smll.202311033.
17. Cai J, Xu J, Ye Z, Wang L, Zheng T, Zhang T, et al. Exosomes Derived From Kartogenin-Preconditioned Mesenchymal Stem Cells Promote Cartilage Formation and Collagen Maturation for Enthesis Regeneration in a Rat Model of Chronic Rotator Cuff Tear. Am J Sports Med. 2023;51:1267–76. doi: 10.1177/03635465231155927.
18. Jenner F, Wagner A, Gerner I, Ludewig E, Trujanovic R, Rohde E, et al. Evaluation of the Potential of Umbilical Cord Mesenchymal Stromal Cell–Derived Small Extracellular Vesicles to Improve Rotator Cuff Healing: A Pilot Ovine Study. Am J Sports Med. 2023;51:331–42. doi: 10.1177/03635465221145958.
19. Kim H, Shim IK, Choi JH, Lee ES, Lee YN, Jeon IH, et al. Extracellular Vesicles Delivered by Injectable Collagen Promote Bone–Tendon Interface Healing and Prevent Fatty Degeneration of Rotator Cuff Muscle. Arthroscopy. 2022;38:2142–53. doi: 10.1016/j.arthro.2022.01.008.
20. Tong X, Xu Y, Zhang T, Deng C, Xun J, Sun D, et al. Exosomes from

CD133+ human urine-derived stem cells combined adhesive hydrogel facilitate rotator cuff healing by mediating bone marrow mesenchymal stem cells. J Orthop Translat. 2023;39:100–12. doi: 10.1016/j.jot.2023.02.002.
21. Ren Y, Zhang S, Wang Y, Jacobson DS, Reisdorf RL, Kuroiwa T, et al. Effects of purified exosome product on rotator cuff tendon-bone healing in vitro and in vivo. Biomaterials. 2021;276:121019. doi: 10.1016/j.biomaterials.2021.121019.
22. Zhang X, Han Z, Han K, Zhang H, Huang J, Huangfu X, et al. Loading Mesenchymal Stem Cell–Derived Exosomes Into a Traditionally Designed Rotator Cuff Patch: A Potential Strategy to Enhance the Repair of Chronic Rotator Cuff Tear Associated With Degenerative Changes. Am J Sports Med. 2022;50:2234–46. doi: 10.1177/03635465221096490.
23. Tan X, Xiao H, Yan A, Li M, Wang L. Effect of Exosomes From Bone Marrow–Derived Mesenchymal Stromal Cells and Adipose-Derived Stromal Cells on Bone-Tendon Healing in a Murine Rotator Cuff Injury Model. Orthop J Sports Med. 2024;12(1):23259671231210304. doi: 10.1177/23259671231210304.
24. He Y, Lu S, Chen W, Yang L, Li F, Zhou P, et al. Exosomes derived from tendon stem/progenitor cells enhance tendon-bone interface healing after rotator cuff repair in a rat model. Bioact Mater. 2024;40:484–502. doi: 10.1016/j.bioactmat.2024.06.014.
25. Zhang X, Wu Y, Han K, Fang Z, Cho E, Hu Y, et al. 3-Dimensional Bioprinting of a Tendon Stem Cell–Derived Exosomes Loaded Scaffold to Bridge the Unrepairable Massive Rotator Cuff Tear. Am J Sports Med. 2024;52:2358–71. doi: 10.1177/03635465241255918.
26. Wang C, Hu Q, Song W, Yu W, He Y. Adipose Stem Cell–Derived Exosomes Decrease Fatty Infiltration and Enhance Rotator Cuff Healing in a Rabbit Model of Chronic Tears. Am J Sports Med. 2020;48:1456–64. doi: 10.1177/0363546520908847.
27. Ponz-Lueza V, Lopiz Y, Arvinius C, et al. Acute and chronic rotator cuff tear: experimental rat model. Animal Models in Medical Research. IntechOpen; 2024. P.1. doi: 10.5772/intechopen.1007511.
28. Chartier C, ElHawary H, Baradaran A, Vorstenbosch J, Xu L, Efanov JI. Tendon: Principles of Healing and Repair. Semin Plast Surg. 2021;35:211–15. doi: 10.1055/s-0041-1731632.
29. Sripathi P, Agrawal DK. Rotator Cuff Injury: Pathogenesis, Biomechanics, and Repair. J Orthop Sports Med. 2024;6:231–48. doi: 10.26502/josm.511500167.
30. Giancola R, Oliva F, Gallorini M, et al. CD200 as a Potential New Player in Inflammation during Rotator Cuff Tendon Injury/Repair: An In Vitro Model. Int J Mol Sci. 2022;23(23):15165.doi: 10.3390/ijms232315165
31. Fang WH, Agrawal DK, Thankam FG."Smart exosomes": a smart approach for tendon regeneration. Tissue Eng Part B Rev. 2022;28:613–25. doi: 10.1089/ten.TEB.2021.0075.
32. Jiang F, Zhao H, Zhang P, et al. Challenges in tendon–bone healing: emphasizing inflammatory modulation mechanisms and treatment. Front Endocrinol (Lausanne). 2024;15:1485876. doi: 10.3389/fendo.2024.1485876.
33. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367(6478):eaau6977. doi: 10.1126/science.aau6977.
34. Kusuma HSW, Widowati W, Gunanegara RF, et al. Effect of conditioned medium from IGF1-induced human Wharton's jelly mesenchymal stem cells on osteoarthritis. Avicenna J Med Biotechnol. 2020;12:172–78.
35. Gissi C, Radeghieri A, Passeri CAL, et al. Extracellular vesicles from rat-bone-marrow mesenchymal stromal/stem cells improve tendon repair in rat Achilles tendon injury model in dose-dependent manner: A pilot study. PLoS One. 2020;15(3):e0229914. doi: 10.1371/journal.pone.0229914
36. Sumapraja K, Hestiantoro A, Liem IK, Boediono A, Z Jacoeb T. Effect of conditioned medium of umbilical cord-derived mesenchymal stem cells as a culture medium for human granulosa cells: an experimental study. Int J Reprod Biomed. 2021;19:1037–1044. doi: 10.18502/ijrm.v19i12.10054.
37. Petit N, Chang YJ, Lobianco FA, et al. Hyaluronic acid as a versatile building block for the development of biofunctional hydrogels: in vitro models and preclinical innovations. Mater Today Bio. 2025;31:101596. doi: 10.1016/j.mtbio.2025.101596.
38. Levy O, Kuai R, Siren EMJ, et al. Shattering barriers toward clinically meaningful MSC therapies. Sci Adv. 2020;6(30):eaba6884. doi: 10.1126/sciadv.aba6884.
39. Wei LX, Cui Y, Lv YL, et al. Lycium barbarum polysaccharide protects BMSCs against cadmium-induced suppression of osteogenic differentiation by modulating autophagy. Ecotoxicol Environ Saf. 2025;295:118148. doi: 10.1016/j.ecoenv.2025.118148.
40. Li X, Zhou X, Huang Z, et al. Study on the mechanism of naringin in promoting bone differentiation: in vitro and in vivo study. Heliyon. 2024;10:e24906. doi: 10.1016/j.heliyon.2024.e24906.
41. Zhang D, Zhao N, Wan C, Du J, Lin J, Wang H. Icariin and icariside II reciprocally stimulate osteogenesis and inhibit adipogenesis of multipotential stromal cells through ERK signaling. Evid Based Complement Alternat Med. 2021;2021:8069930. doi: 10.1155/2021/8069930.
42. Eriani K, Desriani D, Putri VC, et al. The effect of Cissus quadrangularis Salisb. extract on maturation of rat mesenchymal stem cells. Braz J Biol. 2023;83:e270335. doi: 10.1590/1519-6984.270335.
43. Zhou T, Yuan Z, Weng J, et al. Challenges and advances in clinical applications of mesenchymal stromal cells. J Hematol Oncol. 2021;14:24. doi: 10.1186/s13045-021-01037-x.
44. Yan H, Yu T, Li J, et al. Kartogenin improves osteogenesis of bone marrow mesenchymal stem cells via autophagy. Stem Cells Int. 2022;2022:1–15. doi: 10.1155/2022/1278921.
45. Zhu Q, Ma Z, Li H, Wang H, He Y. Enhancement of rotator cuff tendon–bone healing using combined aligned electrospun fibrous membranes and kartogenin. RSC Adv. 2019;9:15582–92. doi: 10.1039/C8RA09849B.
46. Zhao W, Yang J, Kang Y, et al. Animal models of rotator cuff injury and repair: a systematic review. Tissue Eng Part B Rev. 2022;28:1258–73. doi: 10.1089/ten.teb.2022.0034.
47. Yuan T, Lai CT, Yang SQ, et al. The rat as a novel model for chronic rotator cuff injuries. Sci Rep. 2024;14:5344. doi: 10.1038/s41598-024-55281-5.
48. Ahmadzadeh K, Roshdi Dizaji S, Yousefifard M. Lack of concordance between reporting guidelines and risk of bias assessments of preclinical studies: a call for integrated recommendations. Int J Surg. 2023;109:2557–58. doi: 10.1097/JS9.0000000000000475.

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