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# Application of mesenchymal stem cells derived from the umbilical cord or Wharton's jelly and their extracellular vesicles in the treatment of various diseases

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ABSTRACT

Mesenchymal stem cells (MSCs) originating from the umbilical cord (UC) or Wharton's jelly (WJ) have attracted substantial interest due to their potential to augment therapeutic approaches for a wide range of disorders. These cells demonstrate a wide range of capabilities in the process of differentiating into a multitude of cell types. Additionally, they possess a significant capacity for proliferation and are conveniently accessible. Furthermore, they possess a status of being immune-privileged, exhibit minimal tumorigenic characteristics, and raise minimal ethical concerns. Consequently, they are well-suited candidates for tissue regeneration and the treatment of diseases. Additionally, UC-derived MSCs offer a substantial yield compared to other sources. The therapeutic effects of these MSCs are closely associated with the release of nanosized extracellular vesicles (EVs), including exosomes and microvesicles (MVs), containing lipids, microRNAs, and proteins that facilitate intercellular communication. Due to their reduced tumorigenic and immunogenic characteristics, in addition to their convenient manipulability, EVs have arisen as a viable alternative for the management of disorders. The favorable characteristics of UC-MSCs or WJ-MSCs and their EVs have generated significant attention in clinical investigations encompassing diverse pathologies. Therefore, we present a review encompassing current pre-clinical and clinical investigations, examining the implications of UC-MSCs in diverse diseases, including those affecting bone, cartilage, skin, liver, kidney, neural, lung, cardiovascular, muscle, and retinal tissues, as well as conditions like cancer, diabetes, sepsis, and others.

*Abbreviations:* MSCs, mesenchymal stem cells; WJ, Wharton's jelly; EVs, extracellular vesicles; BM, bone marrow; AD, adipose tissue; ESCs, embryonic stem cells; OA, osteoarthritis; OVCFs, osteoporotic vertebral compression fractures; ECM, extracellular matrix; ACECM, acellular cartilage extracellular matrix; IRI, ischemia-reperfusion injury; Con A, concanavalin A; HGF, hepatocyte growth factor; CHIP, carboxyl terminus of HSP70 interacting protein; SCLCs, Schwann cell-like cells; PD, Parkinson disease; AD, Alzheimer's disease; HIE, hypoxic-ischemic encephalopathy; SCI, spinal cord injury; COPD, chronic obstructive pulmonary disease; MI, myocardial ischemia; STZ, streptozotocin; IGF-1, insulin-like growth factor-1; TGF-β1, transforming growth factor beta 1; IPCs, insulin-producing cells; CM, conditioned media.

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## 1. Introduction

Increasing evidence has revealed that mesenchymal stem cells (MSCs) can play influential roles in tissue regeneration and the treatment of various disorders because of their multipotent differentiation and self-renewal capabilities, immunomodulatory effects, effects, and long-term ex vivo proliferation (Ayala-Cuellar et al., 2019). The MSCs can be obtained from paracrine virtually any adult and perinatal/fetal tissues, which include bone marrow (BM), adipose tissue (AD), tooth pulp, synovium, endometrial polyps, and blood, as well as the endometrium, placenta, umbilical cord blood, and Wharton's jelly (WJ) (Kalaszczynska and Ferdyn, 2015; Ribeiro et al., 2013). Adult tissue-derived MSCs, particularly BM, have been the most widely applied stem cell-based therapeutic approach in different disorders (Abbaszadeh et al., 2020). Nonetheless, several drawbacks, including low proliferation and cell contents, along with a painful and invasive separation method connected to a considerable risk of infection and morbidity, have limited their therapeutic application (Mazini et al., 2019; Nancarrow-Lei et al., 2017). Besides, the functional properties of these MSCs can be negatively affected by the donor's age, health, genetics, and exposure to environmental stress (Chu et al., 2020; Brown et al., 2019).

Considering these problems, recent research has focused on perinatal sources such as umbilical cord (UC)-MSCs or WJ-MSCs due to their valuable characteristics like cost-effectiveness, an easy and non-invasive extraction method, high proliferation factors, unlimited availability, and immune-privileged status (Kalaszczynska and Ferdyn, 2015; Abbaszadeh et al., 2020; Bruyn et al., 2010). UC-MSCs are also very young and have suffered less environmental interference (Vieira Paladino et al., 2019). Moreover, UC-MSCs present no risk of tumor formation and seem to have less tendency to form teratomas or induce graft versus host disease after administration (Kamal and Kassem, 2020; El Omar et al., 2014). Therefore, the therapeutic use of these MSCs may not raise any ethical issues.

It has also been established that the advantageous properties of MSCs are mainly related to their extracellular vesicles (EVs), which contain proteins, lipids, mRNAs, and microRNAs and are classified into two main groups, including exosomes and MVs (Abbaszadeh et al., 2022; Hashemi Goradel et al., 2018). EVs derived from MSCs have been extensively used in numerous disorders or tissue injuries and can be great alternatives to their parental cells due to their better safety profiles and ability to store without missing function (Racchetti and Meldolesi, 2021; Fujita et al., 2018).

Accordingly, this review addresses recent preclinical and clinical studies that investigated the therapeutic and regenerative potential of UC-MSCs or WJ-MSCs and their EVs in several diseases, such as bone, cartilage, skin, liver, kidney, neural, lung, cardiovascular, muscle, and retinal injuries, as well as cancer, diabetes, sepsis, and other diseases.

## 2. UC-MSCs and their EVs

The first description of WJ, a gelatinous substance of the UC, by Thomas Wharton, dates back to 1656 (Marino et al., 2019). MSCs were isolated from human WJ of UC for the first time by McElreavey and coworkers in 1991 (McElreavey et al., 1991). There are $1 \times 10^4$ to $5 \times 10^4$ MSCs in each centimeter of WJ tissue, and digestion methods are the most traditional strategies used to isolate the cells (Kalaszczynska and Ferdyn, 2015; Widowati et al., 2019; Liau et al., 2020). However, the tissue explant isolation method showed more advantages than digestion protocols, including lower expenses and higher cell yield, and the obtained MSCs also exhibited a higher proliferation rate (Liau et al., 2020; Hassan et al., 2017).

UC-MSCs are spindle-shaped fibroblast-like cells that express common MSC surface markers like CD73, CD90, CD105, CD13, and CD29 but not CD34, CD45, or CD14 and meet the minimal requirements for MSCs as verified by the International Society for Cellular Therapy (Dominici et al., 2006; Corrao et al., 2012). Besides, UC-MSCs can be great candidates for therapeutic use as they show some properties of embryonic stem cells (ESCs), including ESC-like surface markers such as Tra-1-60, Tra-1-81, SSEA-1, and SSEA-4 as well as Oct-4, Nanog, SSEA-4, and SOX-2 (Marino et al., 2019). Newborn stem cells sourced from perinatal tissues such as UC-MSCs or WJ-MSCs also offer reduced risk of infectious diseases and exposure to toxins compared to adult MSCs. Perinatal MSCs are advantageous due to their easy availability, consistent characteristics, lower risk of donor environmental effects, and immune privileged status (Zhang et al., 2022a).

MSCs possess remarkable immunomodulatory properties crucial for managing autoimmune and inflammatory conditions. They influence both innate and adaptive immune responses through various mechanisms. MSCs inhibit T-cell proliferation and B-cell function, reducing exaggerated immune reactions seen in autoimmune diseases. They also modulate dendritic cells (DCs), crucial in initiating immune responses, helping overall immune response regulation. Additionally, they promote the production and function of regulatory T-cells (Tregs), crucial for immune response regulation and inflammation control. These properties highlight the therapeutic potential of MSCs in managing immune-related disorders (Huang et al., 2022a, 2022b). UC-MSCs produce a rich array of paracrine factors, including growth factors, cytokines, and EVs, which contribute to tissue regeneration and immunomodulation. BM-MSCs and UC-MSCs have displayed comparable phenotypic traits and abilities in modulating the immune system. Mice treated with UC-MSCs appeared to exhibit a slightly higher β-cell mass post-transplantation compared to those treated with BM-MSCs. However, no statistically significant difference was observed between the two treatment groups. Given their abundance and ability to yield higher cell numbers, UC-MSCs seem to hold greater promise for clinical applications compared to BM-MSCs (Zhang et al., 2022a). Moreover, following cytokine stimulation, UC-MSCs exhibited higher levels of prostaglandin E2, IL-6, programmed death-ligand 1, and 2 in an inflammatory environment and demonstrated superior inhibition of T helper 17 cells and induction of Tregs compared to BM-MSCs (Song et al., 2020). In vitro research also revealed that UC-MSCs exhibited greater angiogenic potential when compared to both BM-MSCs and AD-MSCs (Pinto et al., 2020). UC-MSCs have the greatest capacity to inhibit T cell proliferation when compared to MSCs from BM, AD, or the placenta. This is achieved via inducing cell-cycle arrest (G0/G1 phase) and apoptosis, as well as changing the expression of genes linked to apoptosis (Li et al., 2016).

Proteins, lipids, and nucleic acids are among the many biomolecules that MSC-EVs carry and are essential for modifying cellular activities and facilitating intercellular communication. Depending on the parent cell type and the microenvironment, the cargo of EVs can change. These vesicles carry their cargo to target cells by a variety of pathways, including direct fusion, endocytosis, or receptor-mediated uptake, when used in EV-mediated treatment (Chen et al., 2021). MSC-EVs involve various biological processes, including immunomodulation, cell survival, blood coagulation, stem cell differentiation, angiogenesis, autophagy, regeneration, and reproductive biology, offering a promising avenue for therapeutic interventions in various clinical settings (Greening et al., 2015; Ghorbani et al., 2022). MSC-derived EV-based treatments have demonstrated encouraging outcomes in a variety of clinical settings, including tissue engineering, immunotherapy, and regenerative medicine. These treatments have the potential to treat a wide range of diseases, such as tissue damage, autoimmune diseases, neurological problems, and inflammatory conditions.

The major subgroups of EVs are exosomes, which range from 50 to 100 nm in diameter, are purified via centrifugation at 100000 g for 70 min, and can be stored at -80°C (Livshits et al., 2015; Théry et al., 2006). Exosomes encompass various components, including DNA, lipids, RNAs, and cytosolic proteins such as tubulin, actin, and actin-binding proteins. Additionally, they contain annexins and Rab proteins, which play pivotal roles in intracellular transportation and membrane fusion

processes (Wong et al., 2024). Tetraspanins, such as CD9, CD63, CD81, or CD82, are abundantly present in the membrane of exosomes and are frequently utilized as markers for identifying exosomes (Andreu and Yáñez-Mó, 2014). MVs are the other subgroup of EVs, which are categorized by their size of 100–1000 nm and are formed by direct budding from the cell surface. MVs are rich in phosphatidylserine-containing proteins associated with lipid rafts. They are characterized by the presence of CD40 as a surface marker and are filled with sphingomyelin, cholesterol, and ceramide (Nederveen et al., 2021).

UC-MSCs are a promising source for the production of clinical-grade EVs due to their potential therapeutic applications. However, the culture conditions for these MSCs may have an impact on the yield and quality of EVs produced (Bellio et al., 2022a; Fuloria et al., 2021). To optimize the production of UC-MSC clinical-grade EVs, various culture conditions have been explored, such as serum-free media, different oxygen tensions, and various culture substrates. Serum is a commonly used supplement in cell culture media, as it contains growth factors and other nutrients that support cell growth and proliferation (Phelps et al., 2018). However, it has been suggested that serum may also affect the quality and function of EVs produced by UC-MSCs (Binder et al., 2015). Overall, the effects of serum on UC-MSC-derived EV production appear to be context-dependent, and further studies are needed to fully understand the optimal culture conditions for the production of clinical-grade EVs.

## 3. Therapeutic application of UC-MSCs and WJ-MSCs

Increasingly studies have recently assessed the potential role of UC-MSCs or WJ-MSCs in the treatment of several disorders and tissue injuries that are discussed in the following sections (Fig. 1).

### 3.1. Bone disorders

Accumulating evidence suggests that UC-MSCs may serve as promising candidates for bone regeneration, offering a viable alternative to BM-MSCs (Table 1) (Meesuk et al., 2022). For instance, the therapeutic impacts of UC-MSCs were assessed in ovariectomy-induced osteoporosis rat models, which induced osteocalcin synthesis, increased the trabecular bone, and inhibited osteoclast activity (Fu et al., 2018). Human UC (hUC)-MSCs that overexpress RUNX1 exhibit the ability to impede osteoclast formation and osteoblast differentiation. Simultaneously, they foster angiogenesis while suppressing inflammation, ultimately promoting the healing of tendon-bone interactions following Rotator Cuff Injury (RCI) which is a common shoulder injury (Guo et al., 2024). Besides, UC-MSCs overexpressing Wnt10b facilitate the healing of fractures by expediting the transformation of cartilage callus into bone during the remodeling process (Hu et al., 2022).

A systematic review of preclinical models acknowledged that UC-MSCs can be a potential candidate for stem cell therapy for fracture healing and bone regeneration, as an alternative to BM-MSCs. Their proliferative capacity and survival can also be enhanced in combination with 3D scaffolds (Ansari et al., 2018). For example, the in situ-mineralized collagen scaffolds cultured on UC-MSCs can also be considered potential paradigms for the healing of bone damage (Karadas et al., 2014). The osteogenic inductive effect of UC-MSCs has been proven to improve in culture with biomimetic spongy scaffolds from decellularized WJ-extracellular matrix (ECM) via providing more surface area and adhesion sites for the MSCs (Beiki et al., 2018). In an in vitro study, the osteoblastic differentiation capability of hUC-MSCs in combination with hydroxyapatite/bioglass nanocomposite scaffolds was assessed, which demonstrated noticeable potential for bone regeneration (Ebrahimi et al., 2021). In 2020, a study provided evidence that silymarin in combination with hUC-MSCs seeded with PLA/CNT scaffolds could be utilized as a proper means for bone regeneration in rats (Khoobi et al., 2020). Similarly, Puah and coworkers (2021) indicated that peptide conjugates on multilayer graphene oxide films could improve the potential use of hUC-MSCs in bone regeneration (Puah et al., 2021). In a recent study by Cabrera-Pérez et al. (2023), after three weeks, co-culturing BM-MSC and WJ-MSC led to effective osteogenesis. In contrast, WJ-MSC was unable to adhere to bone cells when BM-MSC osteogenic stimuli were not present. 62.5% of mice given WJ-MSC, had effective bone formation in their tibias medullar cavities, according to in vivo research. On the other hand, only 25% of the mice treated with BM-MSC showed signs of newly produced trabeculae (Cabrera-Pérez et al., 2023).

Recently, one randomized, open-label, phase I/IIa trial was carried out at the CHA Bundang Medical Center in Seongnam, Korea. In this

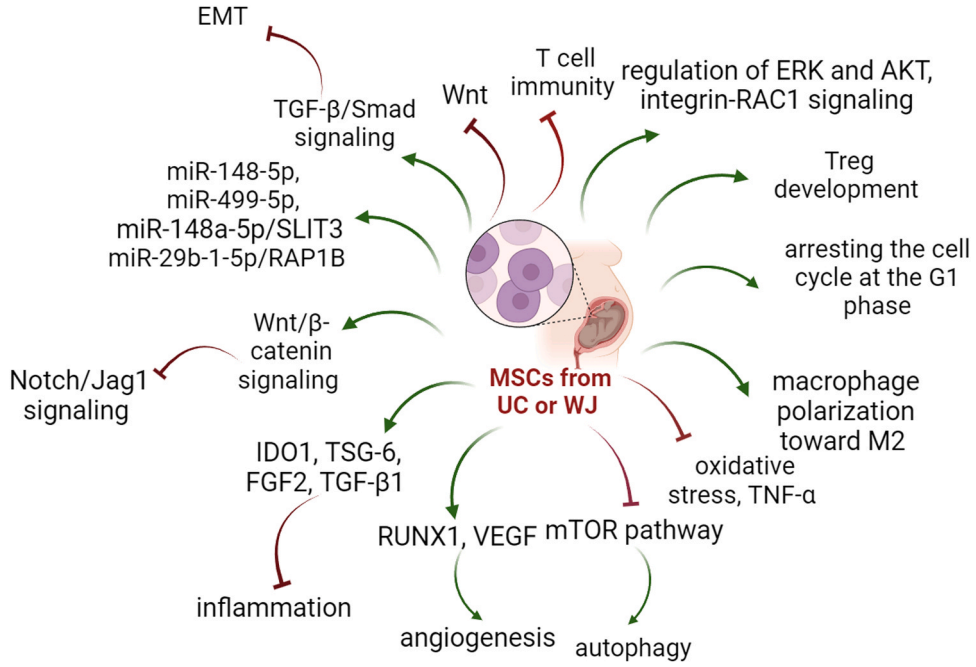


**Fig. 1.** Mesenchymal stem cells derived from Wharton's jelly (WJ-MSCs) or human Umbilical Cord (hUC-MSCs) show therapeutic potential in various diseases by different mechanisms.

**Table 1**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of bone disorders.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| OVX | Rat | WJ-MSCs | Into distal femur | $2.5 \times 10^6$ cells | Could locally stimulate osteocalcin synthesis, increase the trabecular bone, and inhibit osteoclast activity | (Fu et al., 2018) |
| RCI | Rat | hUC-MSCs overexpressing RUNX1 | Into tendon-bone junction | - | Inhibited the formation of osteoclasts and differentiation of osteoblasts, promoted angiogenesis, and inhibited inflammation | (Guo et al., 2024) |
| Bone fracture | Rat | hUC-MSCs overexpressing Wnt10b | Into the injured site | $1 \times 10^5$ cells | Enhanced the osteogenic differentiation of PSCs and increased blood vessel growth. | (Hu et al., 2022) |
| Bone defect | In vitro | WJ-MSCs/ biomimetic spongy scaffolds | - | $2 \times 10^5$ cells | Induced osteogenic differentiation of WJ-MSCs, possibly through activating integrins and subsequently conventional intracellular signaling pathways | (Beiki et al., 2018) |
| Bone defect | In vitro | hWJ-MSCs/ HAp/BG scaffold | - | - | Showed significant potential for bone repair applications in tissue engineering | (Ebrahimi et al., 2021) |
| Bone defect | Rat | hWJ-MSCs/ PLA/CNT scaffold | Into the injured site | - | Can be used as a suitable method for the process of osteogenesis and bone repair | (Khoobi et al., 2020) |
| Bone defect | In vitro | WJ-MSCs on the peptide/m-GO films | - | - | Provided a highly biocompatible and multifunctional 2D material to tailor the potential application of WJ-MSCs in bone tissue regeneration | (Puah et al., 2021) |
| OVCFs | Randomize, open-label, phase I/IIa clinical trial | hWJ-MSCs/ teriparatide | Intramedullary<br>Intravenous | $4 \times 10^7$ cells<br>$2 \times 10^8$ cells | Was feasible and tolerable and had a clinical benefit for fracture healing by promoting bone architecture | (Shim et al., 2021) |
| CPT | A case series | hUC-MSC-CM | - | - | Significant functional improvement was achieved | (Kurniawan et al., 2023) |

OVX: ovariectomy-induced osteoporosis; RCI: Rotator cuff injury; GO: graphene oxide; OVCF: osteoporotic vertebral compression fracture; CPT: congenital pseudoarthrosis of tibia; CM: conditioned media

trial, 20 patients who suffer from osteoporotic vertebral compression fractures (OVCFs) were employed to receive teriparatide alone or in combination with UC-MSCs (intramedullary infusion [$4 \times 10^7$ cells] and intravenous infusion [$2 \times 10^8$ cells] after 1 week). Their findings indicated that the combination therapy was feasible and tolerable and could increase the potential for OVCF healing through improving bone architecture (Shim et al., 2021). In a case series conducted by Kurniawan et al. (2023) from 2016 to 2017, six patients with congenital pseudoarthrosis of tibia (CPT) were included and followed up for a mean of 29 months after treatment with the combination of hUC-MSCs and conditioned media (CM) contains major components pivotal for the enhancement of fracture healing. Five out of 6 of the patients experienced primary union. One patient experienced refracture; however, 8 months later, after another implantation and reconstruction were performed, the union eventually occurred. Significant functional improvement was achieved after at least 1 year of follow-up (Kurniawan et al., 2023).

### 3.2. *Cartilage disorders*

Numerous studies have demonstrated the advantageous effects of UC-MSCs in the regeneration of cartilage (Table 2). In 2020, Kusuma and coworkers studied the impact of CM derived from insulin-like growth factor-1 (IGF-1)-treated hUC-MSCs on osteoarthritis (OA) cells. The findings indicated that this therapy may contribute to the regeneration of injured joints in the human chondrocyte OA cell model via reducing inflammatory cytokines and the matrix degradation mediator matrix metallopeptidase 3 (Kusuma et al., 2020). In a rat model of temporomandibular joint osteoarthritis, MSCs primed with IFN-γ, characterized by increased expression of IDO1, TSG-6, and FGF2, demonstrated strong anti-inflammatory and therapeutic capabilities. This primed state facilitated the amelioration of the inflammatory environment and the promotion of cartilage regeneration. Additionally, when co-cultured with OA chondrocytes from rats, these MSCs induced a reduction in pro-inflammatory factors and factors contributing to the degradation of the ECM (Kim et al., 2024).

WJ-MSCs also showed chondrogenic potential in hyaluronic acid-based hydrogels, indicating their emerging potential in the treatment of injured articular cartilage (Aleksander-Konert et al., 2016). Moreover, human WJ (hWJ)-MSCs in combination with an ACECM scaffold achieved better quality cartilage repair in comparison with microfracture in a caprine model (Zhang et al., 2018a). It has also been reported that a composite scaffold of WJ and chondroitin sulfate loaded with hUC-MSCs could enhance the regeneration of articular cartilage defects in rat knees (Li et al., 2021a). Chitosan-agarose scaffolds also supported the chondrogenesis of hWJ-MSCs for the regeneration of articular cartilage (Merlin Rajesh Lal et al., 2017). In another animal study by Liu et al. (2022), graphene oxide granular lubrication carried by UC-MSCs has been found to enhance chondrocyte secretion, diminish joint inflammation, improve subchondral bone osteoporosis, and contribute to the restoration of cartilage (Liu et al., 2021a).

The effectiveness of hUC-MSCs has been significantly enhanced through combination therapy with other therapeutic agents. The outcomes of one investigation revealed that the combination of rapamycin and hUC-MSCs had a notable positive impact on mitigating the severity of OA in vivo. This combined treatment demonstrated enhanced matrix synthesis and facilitated the process of cartilage repair by enhancing autophagy in chondrocytes, partially by inhibiting the mTOR pathway (Bie et al., 2023). Besides, extracorporeal shockwave combination therapy with UC-MSCs demonstrated synergetic effects in the regeneration of knee OA in rats by induction of RUNX-2, SOX-9, and Collagen Xα1 (Cheng et al., 2019). However, Hsu et al. have demonstrated that shockwave therapy with autologous AD-MSCs is more effective than the hWJ-MSCs in knee OA (Hsu et al., 2020).

A randomized Phase I/II clinical trial (NCT02580695) conducted by Matas et al. in 2018 investigated the therapeutic impacts of intra-

**Table 2**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of cartilage disorders.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| OA | In vitro | IGF1-hWJ-MSC-CM | - | - | Reduced inflammation while repairing injured joint | (Kusuma et al., 2020) |
| Temporomandibular joint OA | Rat | IFN-γ-primed hUC-MSC | - | - | Elevated IDO1, TSG-6, and FGF2 expression exhibited robust anti-inflammatory and therapeutic capacities | (Kim et al., 2024) |
| Articular cartilage defect | In vitro | hWJ-MSC/ HyStem and HyStem-C hydrogels | - | - | Had some degree of chondrogenic potential in HyStem and HyStem-C hydrogels, showing promise for the engineering of damaged articular cartilage | (Aleksander-Konert et al., 2016) |
| Articular cartilage defect | Caprine | hWJ-MSCs/ ACECM scaffold | - | - | Achieved better quality regeneration of hyaline cartilage without cartilage-inducing factor, while retaining the structure and functional integrity of the subchondral bone, compared with MF. | (Zhang et al., 2018a) |
| Knee cartilage defects | Rat | A composite scaffold of WJ and chondroitin sulphate loaded with hUC-MSCs | - | - | Enhanced the regeneration of articular cartilage defects in rat knee | (Li et al., 2021a) |
| Articular cartilage defect | In vitro | hWJ-MSC/ CHAG scaffold | - | - | Supported chondrogenesis of hWJ-MSCs | (Merlin Rajesh Lal et al., 2017) |
| Knee OA | rabbit | UC-MSCs/GO granular lubrication | Into the joint | $5 \times 10^6$ cells | Enhanced chondrocyte secretion, diminished joint inflammation, improved subchondral bone osteoporosis, and contributed to the restoration of cartilage | (Liu et al., 2021a) |
| OA | rabbit | hUC-MSCs/ rapamycin | - | - | Promoted cartilage repair through the mTOR pathway | (Bie et al., 2023) |
| OA | Rat | WJ-MSCs/ ESWT | Intra-articular | $1 \times 10^6$ cells | Demonstrated synergetic effects in regeneration of knee OA by induction of RUNX-2, SOX-9 and Collagen Xα1 | (Cheng et al., 2019) |
| Knee OA | Randomized Phase I/II clinical trial | UC-MSCs | Intra-articular | $2 \times 10^7$ cells | Resulted in an advantageous safety profile and augmented clinical efficacy in the mitigation of chronic pain | (Matas et al., 2019) |
| Knee OA | Randomised, open-label design | hUC-MSC-CM/ hyaluronic acid | Intra-articular | 2 mL | Reduced pain by decreasing MMP-3 and increasing TGF-β1 | (Partan et al., 2023) |

OA: osteoarthritis; GO: graphene oxide

articular administration of UC-MSCs in 26 patients with knee OA which was followed up for 12 months. They were subjected to a randomization process to receive hyaluronic acid (n = 8), a single dosage ($2 \times 10^7$) of UC-MSC (n = 9), or repeated dosages of UC-MSC ($2 \times 10^7 \times 2$; n = 9). The adoption of a repetitive administration protocol of UC-MSC resulted in an advantageous safety profile and augmented clinical efficacy in the mitigation of chronic pain among patients afflicted with knee OA (Matas et al., 2019). Furthermore, the application of both UC-MSC secretome and hyaluronic acid proved to be effective in reducing pain among patients with knee osteoarthritis, with the UC-MSC secretome leading to a more pronounced decrease in pain compared to hyaluronic acid alone. Notably, subjective outcomes significantly favored the use of UC-MSC secretome. Biochemical measurements indicated a trend towards a reduction in MMP-3 levels and an increase in transforming growth factor

**Table 3**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of skin wound.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Skin wound | In vitro/ Mice | WJ-MSC-CM | - | - | Enhanced skin wound healing by increasing skin fibroblast proliferation and migration through paracrine signaling | (Arno et al., 2014) |
| Scarless wound skin | Mice | WJ-MSCs | Transplanted into the injured site | $1 \times 10^5$ cells | Enhance scarless skin wound healing and reduce collagen deposition | (Doi et al., 2016) |
| Diabetic ulcers | Rat | WJ-MSCs | Subcutaneous | - | Effectively accelerated healing | (Nilforoushzadeh et al., 2022) |
| Burnt wounds | In vitro | EGCG primed hWJ-MSCs | - | - | Could enhance therapeutic potential in the burnt tissue through regulation of ERK and AKT signaling pathways | (Butt et al., 2020) |
| Diabetic wound ulcers | Rat | WJ-MSCs/ PF-127 plus SAP | Transplanted onto the wound site | $2 \times 10^6$ cells | Enhanced cutaneous wound healing via improving cell survival, angiogenesis, and the macrophage polarization toward M2 type | (Jiao et al., 2021) |
| Scarless wound skin | Mice | WJ-MSCs/ decellularized amniotic membrane scaffold | Intradermal | $1 \times 10^6$ cells | Caused wound healing, hair growth, and decreased scar formation | (Sabapathy et al., 2014) |
| Chronic diabetic ulcers | Randomized clinical trial | WJ-MSCs/ amniotic membrane scaffold | Transplanted onto the wound site | $2 \times 10^6$ cells | The wound healing time and wound size significantly decreased | (Hashemi et al., 2019) |
| Dermolipectomy chronic ulcer | Case report | WJ-MSCs | - | - | Induced scar formation and neovascularization, as well as the decrease of infiltrated leukocytes and proinflammatory cytokines. | (Mejía-Barradas et al., 2019) |

beta 1 (TGF-β1), although statistical significance was not reached in these changes (Partan et al., 2023).

### 3.3. Skin wounds

UC-MSCs have been extensively researched and recognized as a promising source for the promotion of skin wound healing (Table 3). According to Arno and colleagues' study, WJ-MSCs enhanced skin wound healing in a murine model by enhancing skin fibroblast proliferation and migration through paracrine signaling (Arno et al., 2014). In 2016, Doi et al. established that WJ-MSCs could enhance scarless skin wound healing and reduce collagen deposition in a murine model (Doi et al., 2016). In a recent study in 2022, Nilforoushzadeh et al. also revealed that subcutaneous administration of WJ-MSCs could considerably promote wound healing in diabetic rat models (Nilforoushzadeh et al., 2022).

Butt et al. (2020) have investigated the effect of epigallocatechin-3-gallate on the therapeutic implications of hWJ-MSCs against in vitro heat stress, which suggested their enhanced therapeutic potential in the burnt tissue through regulation of ERK and AKT signaling pathways (Butt et al., 2020). In a recent report, transplantation of WJ-MSCs loaded onto PF-127 hydrogel and sodium ascorbyl phosphate enhanced cutaneous wound healing in type 2 diabetic rats via improved cell survival, angiogenesis, and macrophage polarization toward M2 type (Jiao et al., 2021). The intradermal administration of WJ-MSCs cultured on a decellularized amniotic membrane scaffold into SCID mice illustrated significantly better wound healing, increased hair growth, and decreased scar formation (Sabapathy et al., 2014).

One randomized clinical trial has also been designed to investigate the healing impact of WJ-MSCs grown on biological scaffolds on five subjects suffering from chronic diabetic skin ulcers. The MSCs were injected three times into each patient, and they were followed up for a month. According to the results, healing time and ulcer size have been considerably diminished (Hashemi et al., 2019). In a case report study, WJ-MSCs were infused into a patient suffering from a chronic ulcer caused by dermolipectomy, which contributed to the reduction of inflammatory cytokines and leukocyte infiltration along with an increase in neovascularization and scar formation (Mejía-Barradas et al., 2019).

### 3.4. Liver diseases

The ability of UC-MSCs to undergo differentiation into endodermal lineages, particularly hepatocyte-like cells, positions them as an appealing alternative for the treatment of liver diseases (Table 4) (Kim et al., 2013; Afshari et al., 2020). Borhani-Haghighi et al. (2015) have reported the ability of WJ-MSCs to differentiate into hepatocyte-like cells via permeabilization of them in the presence of HepG2 cell extract (Borhani-Haghighi et al., 2015). The outcomes of a study conducted by Pan and coworkers (2021) who transplanted hWJ-MSCs into a concanavalin A (Con A)-induced fulminant hepatitis mouse model indicated that the MSCs could significantly alleviate hepatitis via suppressing T cell immunity (Pan et al., 2021). Additionally, the regenerative and hepatoprotective effects of intravenous administration of $5 \times 10^5$ WJ-MSCs have been investigated in murine models with galactosamine-induced acute liver injury, which could ameliorate hepatotoxicity (Ramanathan et al., 2017). Recently, it has been found that the transplantation of WJ-MSCs into rats with liver fibrosis can enhance liver function and decrease inflammation and fibrosis in the liver, by possibly targeting TGF-β1 and its downstream gene products (Li et al., 2023). It has also recently been discovered that treatment with hUC-MSC led to a substantial enhancement in liver function and the mitigation of liver fibrosis in mice induced with CCl4. This improvement was attributed to the inhibition of hepatic stellate cell activation through modulation of the miR-148a-5p/SLIT3 pathway (Yuan et al., 2023). The treatment with hUC-MSCs has been shown to inhibit hepatic stellate cell activation, provide protection to hepatocytes, and alleviate liver fibrosis induced by bile duct ligation in mice. This therapeutic effect is associated with the up-regulation of miR-148–5p expression and the inhibition of the Notch signaling pathway (Zhou et al., 2022).

It has also been shown that WJ-MSCs pretreated with Vitamin E significantly attenuated CCl4-induced hepatocyte injury in vitro and a rat model of liver fibrosis by suppressing oxidative stress, inflammation, and fibrosis (Baig et al., 2021). Aleahmad and coworkers found that a heparinized collagen 3D scaffold could accelerate hepatocyte differentiation of WJ-MSCs (Aleahmad et al., 2017). Another experiment investigated the therapeutic impact of hWJ-MSCs in combination with praziquantel in a mouse model of Schistosoma mansoni-induced liver fibrosis, which resulted in better anti-fibrotic effects compared to using

**Table 4**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of liver diseases.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Fulminant hepatitis | In vitro | hWJ-MSCs | - | - | Could alleviate the hepatitis by suppressing the T cell immunity | (Pan et al., 2021) |
| Galactosamine induced acute liver injury | Mice | WJ-MSCs | Intravenous | $5 \times 10^5$ cells | Ameliorated the hepatotoxicity | (Ramanathan et al., 2017) |
| Liver fibrosis | Rat | hUC-MSCs | Intravenous | $2 \times 10^6$ cells | Improved liver function and reduced the inflammatory activity and fibrosis of the liver by targeting TGF-β1 and its downstream gene products | (Li et al., 2023) |
| Liver fibrosis | Mice | hUC-MSCs | Intravenous | $1 \times 10^6$ cells | Inhibited the activation of HSCs through the miR-148a-5p/SLIT3 pathway and alleviated liver fibrosis. | (Yuan et al., 2023) |
| Liver fibrosis | Mice | hUC-MSCs | Intravenous | $1 \times 10^6$ cells | Inhibited HSCs activation, protected hepatocytes, and alleviated liver fibrosis by up-regulating the expression of miR-148–5p and inhibiting the Notch signaling pathway | (Zhou et al., 2022) |
| CCl4-induced hepatocyte injury | In vitro | WJ-MSCs | - | - | Attenuated CCl 4-induced hepatocyte injury in vitro and liver fibrosis in vivo | (Baig et al., 2021) |
| Liver fibrosis | Rat | | Intravenous | $0.25 \times 10^6$ cells | | |
| Liver fibrosis | Mice | WJ-MSCs/ praziquantel | Intra-hepatic | $1.5\times 10^6$ cells | Resulted in better anti-fibrotic effects compared to using each alone | (Hammam et al., 2016) |
| Chronic hepatitis B | Clinical study | UC-MSCs | - | - | UC-MSC transfusion is clinically safe and could improve liver function and reduce ascites in patients with decompensated LC | (Zhang et al., 2012) |
| ACLF | Clinical study | UC-MSC | Intravenous | $0.5 \times 10^6$ | No significant side effects were observed during the trial and it increased the survival rates in ACLF patients; reduced the model for end-stage liver disease scores; increased serum albumin, cholinesterase, and prothrombin activity; and increased platelet counts | (Shi et al., 2012) |

HSCs: hepatic stellate cells; ACLF: acute-on-chronic liver failure

each agent alone (Hammam et al., 2016).

A nonrandomized controlled experiment with 45 chronic hepatitis B patients with decompensated liver cirrhosis was carried out by Zhang et al. (2012). WJ-MSC treatment was administered to thirty patients, while saline was given as a control to the remaining fifteen individuals. The scientists reported that WJ-MSC treatment is safe for patients and significantly reduced ascites volume while improving liver function (Zhang et al., 2012). Besides, an open-labeled Phase I/II trial has reported on the safety and effectiveness of WJ-MSC transfusion in patients with hepatitis B virus-associated acute on chronic liver failure (ACLF). In ACLF patients, there was a significant increase in survival rates, improvements in liver function, and a decrease in a model of end-stage liver disease scores. No notable adverse effects were noted throughout this trial (Shi et al., 2012).

### 3.5. Kidney diseases

UC-MSCs have the potential to ameliorate kidney and podocyte injury in mice with lupus nephritis by suppressing the TGF-β1 pathway (Huang et al., 2022a). Du and colleagues have also illustrated that WJ-MSC therapy can exert valuable effects on acute or chronic kidney injury through endocrine mechanisms and suppressing renal fibrosis (Table 5). Furthermore, activated Akt signaling in tubular epithelial cells contributed to the reduction of apoptosis, increase of proliferation, and induction of endogenous hepatocyte growth factor (HGF) (Du et al., 2012, 2013).

A recent study conducted by Ali et al. (2021) found that the carboxyl terminus of HSP70-interacting protein (CHIP)-overexpressing WJ-MSCs could suppress hyperglycemia-induced oxidative stress in diabetic rats with kidney injuries (Ali et al., 2021a). In addition, WJ-MSCs seeded in a decellularized kidney scaffold ameliorated renal fibrosis by reducing EMT via the TGF-β/Smad signaling pathway following subtotal nephrectomy in rats (Hu et al., 2020a).

### 3.6. Neurological diseases

UC-MSCs or WJ-MSCs hold promise as potential therapeutic agents capable of interrupting neurological disease processes and thereby limiting disease progression (Table 6). Equbal et al. (2021) have recently indicated that WJ-MSCs could efficiently differentiate into neuronal-like cells in a two-stage process, which could be a suitable option for application in regenerative medicine (Equbal et al., 2021). Another recent study by Tomecka et al. (2021) displayed that the hWJ-MSCs are appropriate cell sources for use in tissue regeneration and have neuroprotective potentials; however, a 5% oxygen level appeared to create a more suitable condition for hWJ-MSC proliferation (Tomecka et al., 2021). Results of a study by Jalali et al. (2021) elucidated that intravenous transplantation of hWJ-MSCs could improve motor disturbances in a rat model of Parkinson disease (PD). Nevertheless, they found that hWJ-MSC therapy in combination with L-dopa-carbidopa had the best results in the treatment of PD due to the augmented tyrosine hydroxylase activity and released dopamine from dopaminergic neurons (Jalali et al., 2021). In another study conducted by Xie et al. (2016), WJ-MSC therapy suppressed pro-inflammatory cytokines, relieved memory deficits, and decreased amyloid-β deposition in an APP/PS1 mouse model, suggesting its potential role in the treatment of Alzheimer's disease (AD) (Xie et al., 2016). Besides, SPIONs-labeled WJ-MSCs were magnetically delivered to the hippocampus of the brain in rats with AD and resulted in memory and cognitive enhancement via reducing the degeneration of neurons and improving cholinergic functions. The authors also suggested that magnetically targeted cell delivery is a safe and valuable alternative to the invasive direct MSC injection method for regeneration (Hour et al., 2020). Besides, hWJ-MSC therapy was revealed to regulate inflammation by inducing Treg development in sciatic nerve-injured mice (Wang et al., 2020). Furthermore, a similar experiment proposed that hWJ-MSC therapy can accelerate sciatic nerve injury in mice better than human adipocyte-derived stem cells through upregulation of neurotrophic factor expression (Wang et al., 2019). Mohamadi and coworkers (2019) also found that, because of their ability to inhibit the NLRP1 inflammasome, intrathecal administration of WJ-MSCs attenuated spinal cord injury (SCI) in the rat model (Mohamadi et al., 2019). It has also been proven that the regenerative potential of hWJ-MSCs in SCI is dose-dependent and facilitated by repeated transplantation (Krupa et al., 2018). It has been suggested that hWJ-MSCs can differentiate into neurospheres via the Wnt3A signaling pathway. The locomotion and tissue regeneration of rats with SCI who received neurosphere transplantation were superior to those who did not receive the transplantation (Somredngan et al., 2023).

Another study assessed the effect of combined WJ-MSCs and nerve guidance conduit, which brought remarkable benefits for nerve regeneration through enhancing neurotrophic and angiogenic factors (Shalaby et al., 2017). Recently, Won et al. (2020) found that the use of Fibulin 5, hWJ-MSC-derived paracrine factor, improved Schwann cell myelination defects via the integrin-RAC1 signaling pathway (Won et al., 2020). Xenografting of hWJ-MSCs has also ameliorated mouse spinocerebellar ataxia type 1 (Tsai et al., 2019). The therapeutic potential impact of intra-hippocampal transplantation of the hWJ-MSCs has also been shown in rats with pilocarpine-induced epilepsy, which was associated with their neuroprotective and anti-inflammatory properties (Huang et al., 2016). Additionally, it has been reported that thrombin-preconditioned hWJ-MSCs might considerably enhance severe hypoxic-ischemic encephalopathy (HIE)-induced brain injury in rodent models and were proven to have no toxic and tumorigenic effects

**Table 5**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of kidney diseases.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Lupus nephritis | Mice | hUC-MSCs | Intravenous | $2 \times 10^5$ cells | Improved kidney injury and podocyte injury by inhibiting the TGF-β1 pathway | (Zhang et al., 2012) |
| IRI induced AKI | Rat | WJ-MSCs | Intravenous | $2 \times 10^6$ cells | Alleviated acute kidney injury, thereby rescuing the ensuing fibrotic lesions in an endocrine manner. The Akt signal in impaired tubular cells was reinforced, facilitating cell resistance to apoptosis and cell proliferation | (Du et al., 2012) |
| AKI | Rat | WJ-MSCs | Intravenous | $2 \times 10^6$ cells | Contributed to tubular EMT delay and the alleviation of renal fibrosis | (Du et al., 2013) |
| Diabetes-induced kidney injury | Rat | CHIP-overexpressing WJ-MSCs | - | - | Suppressed hyperglycemia-induced oxidative stress and conferred resistance to MAPK-induced apoptosis and fibrosis | (Ali et al., 2021a) |
| Renal fibrosis | Rat | WJ-MSCs/ decellularized kidney scaffold | Intravenous | $2.5 \times 10^7$ cells | Ameliorated renal fibrosis through decreasing EMT by the TGF-β/Smad signaling pathway after subtotal nephrectomy | (Hu et al., 2020a) |

AKI: acute kidney injury; IRI: ischemia-reperfusion; CHIP: Carboxyl terminus of HSP70 interacting protein;

**Table 6**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of neurological diseases.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| PD | Rat | hWJ-MSCs | Intravenous | $1 \times 10^6$ cells | Improved motor activity | (Jalali et al., 2021) |
| AD | Mice | hWJ-MSCs | Intravenous | - | Alleviated the memory decline and reduced amyloid-β deposition through modulation of neuroinflammation | (Xie et al., 2016) |
| AD | Rat | SPIONs-labeled hWJ-MSCs | Intravenous | - | Improved cognitive impairments in AD by attenuating degeneration of neurons and boosting cholinergic functions in the hippocampus | (Hour et al., 2020) |
| Injured sciatic nerve | Mice | hWJ-MSCs | - | $5 \times 10^5$ cells | Regulated inflammation by inducing Treg development | (Wang et al., 2020) |
| SCI | Rat | WJ-MSCs | Intrathecal | - | Improved motor function recovery | (Mohamadi et al., 2019) |
| SCI | Rat | hWJ-MSC-derived neurospheres | Into the spinal cord | $1 \times 10^5$ cells | Improved tissue regeneration | (Somredngan et al., 2023) |
| SCA1 | Mice | hWJ-MSCs | Into the cerebella | $1 \times 10^6$ cells | Ameliorated motor symptoms and cerebellar degeneration | (Tsai et al., 2019) |
| Epilepsy | Rat | hUC-MSCs | Intra-hippocampal | $1 \times 10^5$ cells | Decreased neuron and interneuron loss, suppressed brain inflammation | (Huang et al., 2016) |
| HIE | Mice | Thrombin-preconditioned-hWJ-MSCs | Into the cerebral ventricle | $1 \times 10^5$ cells | This therapy was not oncogenic and no abnormal changes or findings were observed | (Noh et al., 2021) |
| HIE | Case clinical study | WJ-MSCs | Intrathecal, Intramuscular, Intravenous | $1 \times 10^6$ cells | After stem cell infusions, progressive improvements were shown in his neurological examination, neuroradiological, and neurophysiological findings | (Kabataş et al., 2018) |
| Amyotrophic lateral sclerosis | Clinical study | WJ-MSCs | Intrathecal | $0.42 \times 10^6$ cells | It was safe | (Barczewska et al., 2019) |

PD: Parkinson's disease; AD: Alzheimer's disease; SCA1: spinocerebellar ataxia type 1; HIE: hypoxic-ischaemic encephalopathy

(Noh et al., 2021).

Generation of neural stem cells from hWJ-MSCs is also possible in a 2D culture (Kruminis-Kaszkiel et al., 2020). It has also been suggested that 3D alginate cell culture is an effective scaffold for neuronal differentiation of WJ-MSCs (Hosseini et al., 2015). The WJ-MSCs seeded on 3D nanostructural and PCL/collagen scaffolds could be beneficial candidates for inducing motor neurons and neuroprotection (Bagher et al., 2016).

A 16-year-old child with HIE was given an intrathecal, intramuscular, and intravenous infusion of WJ-MSCs in a controlled case clinical trial. The HIE patient's clinical results progressed, indicating the safety and viability of triple route WJ-MSC transplants (Kabataş et al., 2018). Furthermore, to evaluate the safety of intrathecal infusion of WJ-MSCs ($0.42 \times 10^6$ cells, twice) in amyotrophic lateral sclerosis therapy, 43 patients were recruited and followed up for 6 months, which was well tolerated (Barczewska et al., 2019).

### 3.7. Pulmonary disease

The impact of hWJ-MSCs has been explored in a chronic obstructive pulmonary disease (COPD) mouse model by Cho et al. (2019) (Table 7). They suggested that injection of hWJ-MSCs has no significant effect on COPD (Cho et al., 2019). Park et al. (2019) reported that intravenous infusion of pioglitazone-treated WJ-MSCs ($1 \times 10^4$) per COPD mouse model, produced better lung regeneration in comparison with non-augmented WJ-MSCs (Park et al., 2019). Recently, the hWJ-MSC-secretome was revealed to have antiviral potential against SARS-CoV-2, which was mainly mediated by virucidal and anti-replication mechanisms (Hussein et al., 2022). Besides, hUC-MSCs, which are engineered to overexpress CXCR7, play a crucial role in the treatment of pulmonary fibrosis associated with acute respiratory distress syndrome (ARDS). This therapeutic effect is achieved by suppressing the Notch/Jag1 pathway through the Wnt/β-catenin signaling pathway (Xiao et al., 2023).

Recently, Saleh and coworkers (2021) reported a study where $15 \times 10^7$ WJ-MSCs were intravenously infused three times into five patients with severe COVID-19. According to the findings, the trend of lung tests was mostly improved, the inflammation was reduced, and no serious adverse events were observed in these patients (Saleh et al., 2021).

### 3.8. Cardiovascular diseases

The valuable potential of WJ-MSCs in the treatment of cardiovascular diseases has been reported in several studies (Table 8). In a comparative study by Lopez and colleagues (2013), the intravenous injection of WJ-MSCs showed more successful effects than BM-MSCs in

**Table 7**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of pulmonary diseases.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| COPD | Mice | h-MSCs | Intravenous | $5 \times 10^4$ cells | Showed pulmonary regenerative effects | (Cho et al., 2019) |
| COPD | Mice | Pioglitazone-treated WJ-MSCs | Intravenous | $1 \times 10^4$ cells | Produced lung regeneration | (Park et al., 2019) |
| SARS-CoV-2 | In vitro | hWJ-MSC-secretome | - | - | Showed antiviral potency | (Hussein et al., 2022) |
| ARDS | In vitro | hUC-MSCs overexpressing CXCR7 | - | - | Reduced lung fibrosis by inhibiting Jag1 via suppression of the Wnt/β-catenin pathway under the chemotaxis of SDF-1. | (Xiao et al., 2023) |
| COVID-19 | Clinical study | hWJ-MSCs | Intravenous | $15 \times 10^7$ cells | The trend of tests was generally improving, and a reduction in inflammation was occurred | (Saleh et al., 2021) |

ARDS: acute respiratory distress syndrome; ALI: acute lung injury

**Table 8**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of cardiovascular diseases.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| MI | Rat | WJ-MSCs | Intravenous | 3–10 × $10^6$ cells | Showed more successful effects than BM-MSCs in improvement of cardiac function | (López et al., 2013) |
| MI | Porcine | WJ-MSCs | Intravenous | - | Enhanced left ventricular function, perfusion, and remodeling through their anti-apoptotic and anti-fibrotic effects | (Liu et al., 2016) |
| Dilated cardiomyopathy | Rat | WJ-MSCs | Intravenous | 1 × $10^6$ cells | Reduced interstitial fibrosis and improve cardiac function through attenuating TNF-α and TGF-β1/ERK1/2 signaling pathway | (Zhang et al., 2018b) |
| MI | Miniswine | WJ-MSCs | Into ischemic site | 4 × $10^7$ cells | Enhanced myocardial function, differentiated into cardiomyocytes and vascular endothelial cells and reduced apoptosis and fibrosis, and improving ventricular remodeling and function | (Zhang et al., 2013) |
| Doxorubicin-induced cardiac injury | Mice | Epigenetic modified WJ-MSCs | Intravenous | 1 × $10^6$ cells | Developed WJ-MSCs' differentiation into the cardiomyocytes by inhibiting Wnt | (Bhuvanalakshmi et al., 2017) |
| Diabetic cardiac damages | Rat | hWJ-MSCs overexpressing CHIP | Intravenous | 1 × $10^7$ cells | Promoted the prophylactic effects | (Ali et al., 2021b) |
| MI | Rabbit | hWJ-MSCs/IGF-1 | Intra-myocardial | - | Improved cardiac function and promoted angiogenesis | (Rabbani et al., 2018) |
| AMI | Clinical study | WJ-MSCs | - | 30 × $10^6$ | This study demonstrated the feasibility and procedural safety of WJMSC use as off-the-shelf cellular therapy in human AMI | (Musialek et al., 2015) |
| AMI | Clinical study | WJ-MSCs | Intracoronary | 6 × $10^6$ | It was safe in treating patients with an AMI attack and could significantly improve myocardial viability and heart function | (Gao et al., 2015) |

MI: myocardial ischemia; CHIP: carboxyl terminus of Hsc70 interacting protein

improving cardiac function in a rat model of myocardial ischemia (MI) (López et al., 2013). In another study, porcine models with chronic MI were divided into two control and WJ-MSC-treated groups. The authors acknowledged that multiple intravenous administrations of WJ-MSCs enhanced left ventricular function, perfusion, and remodeling through their anti-apoptotic and anti-fibrotic effects (Liu et al., 2016). Additionally, WJ-MSCs were able to reduce interstitial fibrosis and improve cardiac function in a rat model of dilated cardiomyopathy through attenuating TNF-α and TGF-β1/ERK1/2 signaling pathways (Zhang et al., 2018b). The impact of hWJ-MSCs on myocardial and cardiac regeneration of 18 miniswine models with acute MI was also assessed. The miniswines were divided into three groups (n=6 in each): the controls, the PBS group, and the WJ-MSCs treated group. According to the findings of this study, transplantation of WJ-MSCs into the infracted area considerably enhanced myocardial function and they were able to differentiate into cardiomyocytes and vascular endothelial cells. These MSCs also had abilities to reduce apoptosis and fibrosis and improve ventricular remodeling and function (Zhang et al., 2013). Another experiment by Pu et al. (2017) has highlighted the potential of WJ-MSCs as an appropriate cell source for cardiovascular tissue regeneration in comparison to amniotic membrane-derived MSCs due to their higher proliferation, self-renewing, and anti-coagulation abilities (Pu et al., 2017). However, Hoe Ng et al. proposed that hWJ-MSCs can enhance the growth kinetics of cardiomyocyte differentiation in aged murine cardiac c-kit cells; however, the impact was not significant (Ng et al., 2019).

It has also been demonstrated that epigenetic modification can develop WJ-MSCs' differentiation into cardiomyocytes by inhibiting Wnt in a mouse model of cardiac injury (Bhuvanalakshmi et al., 2017). Results of an in vitro study revealed that WJ-MSCs altered to over-express anti-fibrotic genes may provide an emerging approach to protect against cardiac fibrosis (Nimsanor et al., 2019). CHIP-overexpressed WJ-MSCs have been shown to reduce hyperglycemia-induced apoptosis and oxidative stress in embryo-derived cardiac cell lines and streptozotocin (STZ)-induced diabetic rats and ameliorate hyperglycemia-induced cardiac injury (Ali et al., 2021b). The intra-myocardial injection of hWJ-MSCs in combination with IGF-1 was also proven to play an essential role in improving cardiac function and promoting angiogenesis in a rabbit myocardial infarction model (Rabbani et al., 2018).

Musialek et al. (2015) used WJ-MSCs to treat 10 acute myocardial infarction (AMI) patients, demonstrating the safety and viability of these MSCs as an over-the-counter medicinal treatment (Musialek et al., 2015). Similarly, Gao et al. (2015) conducted a double-blind, randomized controlled experiment to examine the safety and effectiveness of WJ-MSCs in the management of patients with ST-elevation AMI. A total of 116 individuals were enrolled, and they were followed up after 18 months after randomly receiving intracoronary injections of WJ-MSCs or a placebo several times. WJ-MSCs were found to be safe in AMI therapy and to successfully enhance cardiac function and myocardial viability (Gao et al., 2015).

### 3.9. Muscular disorders

An in vitro study by Mesure et al. (2017) has established that TGF-β1 and ascorbic acid are successful stimulators in differentiating WJ-MSCs into the smooth muscle phenotype (Table 9) (Mesure et al., 2017). It has also been reported that Sdf-1 elevates the migration of WJ-MSCs when transplanted into regenerating muscle (Kowalski et al., 2017). Kwon et al. (2016) reported that co-culture of WJ-MSCs and WJ-MSC-derived XCL1 protein with skeletal myoblast cell lines (C2C12) contributes to their apoptosis. In vivo, results also demonstrated that WJ-MSCs significantly recovered the zebrafish skeletal muscle defects by secreting XCL1 (Kwon et al., 2016). The hWJ-MSCs with high Aurora Kinase expression have also had potential therapeutic effects against muscular disorders (Kim et al., 2022).

Recently, Park et al. (2021) proposed that intravenous administration of WJ-MSCs into a Duchenne muscular dystrophy mouse model could result in a reduction of fibrosis via upregulating miR-499–5p (Park et al., 2021). In another experiment, the regenerative role of WJ-MSCs was investigated in a skeletal muscle injury mouse model induced by bupivacaine. Their findings elucidated that the WJ-MSC therapy restored functional impairment by suppressing of neutrophil-mediated inflammation and preventing TGF-β1-induced fibrosis through attenuating ECM components (Su et al., 2019). Moreover, intramuscular or

**Table 9**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of muscular disorders.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Muscular Dystrophy | Mice | WJ-MSC-miR-499–5p | Intravenous | $5 \times 10^3$ to $5 \times 10^5$ cells | Reduced fibrosis | (Park et al., 2021) |
| Skeletal muscle injury | Mice | WJ-MSCs | Intramuscular | $5 \times 10^5$ cells | Restored functional impairment by suppressing of neutrophil-mediated inflammation and preventing TGF-β1-induced fibrosis through attenuating ECM components | (Su et al., 2019) |
| Sarcopenia | Mice | hWJ-MSCs | Intramuscular and intravenous | - | Ameliorated through inhibiting apoptosis and decreasing chronic inflammation | (Wang et al., 2018) |
| Sarcopenia | Mice | hUC-MSCs | Intraperitoneal | $5 \times 10^6$ cells | Prevented muscle diseases | (Wang et al., 2023a) |

intravenous transplantation of hWJ-MSCs ameliorated sarcopenia in a cell-aged mouse model by inhibiting apoptosis and decreasing chronic inflammation in skeletal muscle (Wang et al., 2018). The findings of another research indicated that hUC-MSCs effectively enhanced skeletal muscle strength and performance in two mouse models of age-related sarcopenia (AAS). This improvement is attributed to increased expression of ECM proteins, activation of satellite cells, improvement in autophagy, and prevention of cellular aging (Wang et al., 2023a).

### 3.10. Cancer

Recently, Figen Abatay-Sel and coworkers (2023) demonstrated that WJ-MSCs have a more apoptotic impact on HT-29 cells, and CRC cell lines, in comparison with the umbilical cord blood-MSCs (Table 10) (Abatay-Sel et al., 2023).

Mirabdollahi et al. (2020) have demonstrated that the hWJ-MSC-secretome could prevent the growth of breast cancer cell lines in vitro by modulating hematological parameters. Furthermore, intratumoral transplantation of the hWJ-MSC-secretome contributed to significant inhibition of tumor development, the reduction of tumor size and weight, and the prolonged survival rate in tumor-bearing mice (Mirabdollahi et al., 2020). It has also been demonstrated that WJ-MSC-secretomes inhibited colorectal cancer cell (CRC) growth and improved cell apoptosis via the intrinsic apoptotic pathway (Rezaei--Tazangi et al., 2020). Aslam et al. carried out an in vitro experiment to study the anti-tumor effects of WJ- and BM-MSC-secretomes in glioma cells. According to their findings, the secretomes, particularly those derived from the WJ-MSCs, effectively inhibited U87MG glioma cell growth and migration by arresting the cell cycle at the G1 phase (Aslam et al., 2021). Hendijani and coworkers have also revealed that the hWJ-MSC-secretomes have no proliferative or anti-apoptotic impact on lung cancer cells. However, they demonstrated that this therapy was not tumorigenic (Hendijani et al., 2015a). Hendijani et al. also showed in another investigation that hWJ-MSC-secretomes decreased leukemia cell line proliferation and induced additive cytotoxic impacts when combined with doxorubicin (Hendijani et al., 2015b). The UC-MSC-CM also demonstrated an anti-tumor impact on granulosa tumor cell line (KGN) cells by inducing cell cycle arrest specifically at the G1 phase. Additionally, it effectively suppressed cell migration and invasion while promoting apoptosis in these cells. This anti-tumor effect was achieved by activating the Hippo pathway, ultimately restoring contact inhibition in the cells (Wan et al., 2023).

### 3.11. Autoimmune disease

WJ-MSCs have also applied for the treatment of various autoimmune diseases (Table 11). For instance, Torkaman et al. (2017) found that IFN-γ can be applied as a stimulator of the immunomodulatory characteristics of WJ-MSCs in experimental autoimmune encephalomyelitis mice by elevating Treg cells and reducing the secretion of inflammatory cytokines (Torkaman et al., 2017). Recently, Wei et al. (2023) demonstrated that intravenous administration of $1 \times 10^6$ hUC-MSCs to S100-induced autoimmune hepatitis mice could suppress liver inflammation and ultimately alleviate hepatocyte dysfunction by regulating responses of Th1 and Th17 cells (Wei et al., 2023a).

It has also been recently reported that xeno-free conditions enhanced the immunomodulation and therapeutic effects of WJ-MSCs in mouse models of colitis through upregulating indoleamine 2,3-dioxygenase activity (Kang et al., 2020). In their 2023 study, Liu et al. discovered that hUC-MSCs could be effective in alleviating colon inflammation in patients with inflammatory bowel disease (IBD). This therapeutic impact was attributed to the reshaping of T-cell immune homeostasis, achieved by remodeling the composition and diversity of gut flora. Notably, there was an upregulation in the abundance of bacteria producing short-chain fatty acids (SCFAs), which are known for their anti-inflammatory properties. Additionally, targeted metabolomics revealed an increase in SCFAs production following the administration of MSCs, and a significant positive correlation was observed between specific changes in bacterial composition and the levels of SCFAs (Liu et al., 2023).

**Table 10**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of cancer.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| ` Breast cancer | In vitro/ mice | hWJ-MSC-secretome | Intratumoral | 20 mg/mL | Inhibited tumor development, reduced tumor size and weight, and prolonged survival rate in tumor bearing mice | (Mirabdollahi et al., 2020) |
| Colorectal cancer | In vitro | hWJ-MSC-secretome | - | - | Inhibited colorectal cancer cell growth and improved cell apoptosis | (Rezaei-Tazangi et al., 2020) |
| Brain tumor | In vitro | hWJ-MSC-secretome | - | - | Inhibited U87MG glioma cells growth and migration through arresting the cell cycle at the G1 phase | (Aslam et al., 2021) |
| Lung cancer | In vitro | hWJ-MSC-secretome | - | - | Was not tumorigenic and also did not make lung cancer cells resistant to doxorubicin | (Hendijani et al., 2015a) |
| Leukemia | In vitro | hWJ-MSC-secretome | - | - | Exerted cytotoxic effect on leukemia cells | (Hendijani et al., 2015b) |
| Granulosa tumor cell | In vitro | UC-MSC-CM | - | - | Exerted anti-tumor effect by activating Hippo pathway to restore contact inhibition | (Wan et al., 2023) |

TNBC: triple negative breast cancer; AML: acute myeloid leukemia

**Table 11**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of autoimmune diseases.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Encephalomyelitis | Mice | IFN-γ primed hWJ-MSCs | - | - | Reduced proliferation and increased Treg cells as well as decreased secretion and gene expression of inflammatory cytokine | (Torkaman et al., 2017) |
| Autoimmune hepatitis | Mice | hUC-MSCs | Intravenous | $1 \times 10^6$ cells | Attenuated S100-induced hepatitis via modulating Th1 and Th17 Cell responses | (Wei et al., 2023a) |
| IBD | Mice | hWJ-MSCs in a xeno-free medium | Intraperitoneal | $2 \times 10^6$ cells | Had a significantly higher suppressive effect on human peripheral blood-derived T cell proliferation, Th1 and Th17 differentiation, as well as naïve macrophage polarization toward an M1 phenotype | (Kang et al., 2020) |
| IBD | Mice | hUC-MSCs | Intraperitoneal | $1 \times 10^6$ cells | Ameliorated colon inflammation via modulation of gut microbiota-SCFAs-immune axis | (Liu et al., 2023) |
| Psoriasis | Mice | hUC-MSCs | - | - | Alleviated psoriasis through TNF-α/NF-κB/MMP13 pathway | (Ren et al., 2023) |
| Alopecia areata | Clinical trial | hWJ-MSCs | Intradermal | - | Was safe and hair regrowth was observed in all participants | (Czarnecka et al., 2021) |

IBD: inflammatory bowel disease

Moreover, systematically infused hUC-MSCs exert a therapeutic effect on psoriasis through the TNF-α/NF-κB/MMP13 pathway. In the skin lesions of an imiquimod-induced mouse model, elevated expression of MMP13 was observed, but this was downregulated following intravenous infusion of hUC-MSCs. The suppression of MMP13 resulted in the inhibition of keratinocyte proliferation and cell cycle arrest at the G1 stage. Additionally, in vitro co-culturing experiments involving hUC-MSCs with THP-1 were conducted to mimic the fate of systemically infused hUC-MSCs. This co-culture led to a decrease in TNF-α levels in the supernatant. Furthermore, it was determined that TNF-α upregulated MMP13 via the NF-κB pathway in keratinocytes (Ren et al., 2023).

In a study, four subjects suffering from alopecia areata underwent WJ-MSC therapy via a single intradermal administration. According to the findings, this therapy was safe, and hair regrowth was observed in all participants (Czarnecka et al., 2021).

### 3.12. Diabetes

It has been suggested that hWJ-MSCs can enhance diabetes-associated intracavernosal pressure impairment in rats via an increase in paracrine growth factors, indicating a novel emerging therapeutic choice for erectile dysfunction (Table 12) (Wu et al., 2022).

As demonstrated by Sarvestani et al. (2020), intraportal transplantation of WJ-MSCs in combination with insulin could enhance diabetic symptoms in STZ-induced diabetes rats by regulating the level of neuropeptide Y and melanocortin-4 receptor (Sarvestani et al., 2020). Additionally, obestatin has the potential to generate WJ-MSCs into insulin-producing cells (IPCs) and can be an emerging candidate for β-cell therapy in diabetes patients (El-Asfar et al., 2018; Ranjbaran et al., 2018). Another experiment also investigated the differentiation capability of hWJ-MSCs into IPCs before intravenous transplantation into rats with STZ-induced diabetes. The authors acknowledged that the differentiated IPCs were homed to the pancreas and could remarkably ameliorate blood glucose levels in the rats because of the continuous release of insulin. Meanwhile, the administration of undifferentiated hWJ-MSCs enhanced insulitis and regulated inflammation in diabetic rats with a slight progression in blood glucose levels (Hsiao et al., 2020).

Moreover, a recent study acknowledged the possible potential role of hWJ-MSCs as a candidate therapy for diabetes via differentiation into SOX17-expressing cells through Wnt/β-catenin pathway agonists in 3D cultures on PLA/Cs scaffolds (Hoveizi and Tavakol, 2022). Li et al. (2020) have assessed the therapeutic role of WJ-MSCs attached to Fe3O4@polydopamine nanoparticles in rat models with STZ-induced diabetes, demonstrating structural retention in the pancreas and enhanced islet function by their anti-inflammatory and anti-apoptotic properties (Li et al., 2020). It has also been verified that the PRP-PVP-PCL/PCL scaffold is a novel 3D structure, which can release PRP in a phased and gradual manner, leading to a substantial enhancement in the performance of IPCs derived from WJ-MSCs (Hashemi et al.).

A phase 2 clinical trial carried out by Lian et al. (2023) evaluated the safety of hUC-MSC transplantation in 24 patients with type 2 diabetes mellitus. The findings suggested that hUC-MSC transplantation exhibited favorable tolerance and high safety in the treatment of type 2 diabetes mellitus via improving human immunity and suppressing lymphocytes (Lian et al., 2023).

### 3.13. Endometrium damages

In 2017, Shi et al. showed the differentiation capability of WJ-MSCs into endometrium stromal cells (Table 13) (Shi et al., 2017). A recent finding investigated the regenerative impact of hWJ-MSCs on the incisional scar of the uterus in a rat model, which could repair it efficiently by improving the uterine endometrium and myometrium cell

**Table 12**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of diabetes.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Diabetes | Rat | hWJ-MSCs | - | $2 \times 10^7$ cells | Improved diabetic erectile dysfunction through increased production of paracrine growth factors | (Wu et al., 2022) |
| Diabetes | Rat | hWJ-MSCs/insulin | Intraportal | $2 \times 10^6$ cells | Ameliorated diabetes signs by changing the amount of leptin and subsequent changes in the expression of MC4R, NPY, and LEPR. | (Sarvestani et al., 2020) |
| Diabetes | Rat | hWJ-MSCs | Intravenous | $5 \times 10^6$ cells | Improved insulitis and re-balance the inflammatory condition | (Hsiao et al., 2020) |
| Diabetes | Rat | hWJ-MSCs/ Fe3O4@polydopamine nanoparticle | - | - | Improved the islet function, and showed anti-inflammatory effects and the anti-apoptotic capacity | (Li et al., 2020) |
| Diabetes | Phase 2 clinical trial | hUC-MSCs | Intravenous | $1 \times 10^6$ cells | Had good tolerance and high safety | (Lian et al., 2023) |

**Table 13**
The potential role of mesenchymal stem cells derived from umbilical cord or Wharton's jelly in the treatment of endometrium damages.

| Injury | Study model | Type of MSCs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Injured uterine endometrium | Rat | hWJ-MSCs | - | - | Promoted the uterine endometrium and myometrium cells proliferation | (Wang et al., 2021) |
| Endometrial injury | Rat | hUC-MSC-loaded hydrogel | - | - | Promoted the expression of endometrial VEGF through MEK/ERK1/2 signaling pathway and regulated the balance of inflammatory factors | (Zhang et al., 2023a) |
| Endometrial injury | In vitro | hWJ-MSCs | - | - | Promoted angiogenesis and stimulated the proliferation of endometrial stromal cells through regulation of the miR-29b-1–5p/RAP1B axis | (Shi et al., 2020) |

proliferation (Wang et al., 2021). In a rat model of endometrial injury, the administration of an injectable hydrogel loaded with hUC-MSCs notably increased the thickness of the endometrium and enhanced the abundance of blood vessels and glands compared to the control group. Furthermore, the hUC-MSCs-loaded injectable hydrogel effectively mitigated endometrial fibrosis, downregulated the expression of pro-inflammatory factors (IL-1β and IL-6), and upregulated the expression of the anti-inflammatory factor (IL-10). The treatment induced the expression of endometrial VEGF by activating the MEK/ERK1/2 signaling pathway. Importantly, this intervention improved endometrial receptivity to embryos, restoring the embryo implantation rate to levels comparable to the control group. Ultimately, the treatment facilitated pregnancy and live birth in rats with endometrial injury (Zhang et al., 2023a).

It was also demonstrated that circ6401 is implicated in the regeneration of the impaired endometrium stromal cells by WJ-MSCs via regulating the miR-29b-1–5p/RAP1B axis and increasing their proliferation and angiogenesis (Shi et al., 2020). Additionally, the elevated circRNA profile, especially hsa_circRNA_0111659, via WJ-MSCs was proven in the process of repairing the injured endometrium (Sun et al., 2018).

### 3.14. Other disorders

Laroye et al. (2019) compared the therapeutic efficiency of BM-MSCs and WJ-MSCs in a murine cecal ligation and puncture model of sepsis. According to the archived results, BM- and WJ-MSCs modulated leukocyte trafficking and decreased organ dysfunction, however, only WJ-MSCs had more antibacterial properties (Laroye et al., 2019). Besides, WJ-MSC therapy was shown to have protective effects in sepsis-induced renal, liver, and endothelial dysfunctions in rat models by improving the glomerular filtration rate and tubular function, elevating pro-inflammatory markers, as well as inducing a Klotho-deficient state and decreasing expression of NF-κB and renal cell apoptosis (Cóndor et al., 2016). In a rat model of sepsis-induced organ injury, intraperitoneal administration of $1 \times 10^6$ WJ-MSCs exerted beneficial impacts on injured organs via decreasing systemic inflammation. The MSCs reduced apoptosis in the lungs and spleen. Also, they downregulated leukocyte infiltration and pro-inflammatory cytokines, which are mediated by α7 nicotinic acetylcholine receptors (α7nAChRs). In addition, the WJ-MSC therapy suppressed α7nAChRs in the heart and spleen (Capcha et al., 2020). According to the current evidence, WJ-MSCs can differentiate into retinal progenitor cells in vitro (Hu et al., 2013). In a study conducted by Millán-Rivero et al. in 2018, the protective potential of hWJ-MSCs in axotomized rat retinal ganglion cells was confirmed through elevating anti-inflammatory and neurotrophic factors (Millán-Rivero et al., 2018). One prospective, open-label, and phase III clinical trial has also evaluated the advantageous impact of WJ-MSCs on the visual functions of 32 patients with retinitis pigmentosa at Ankara University. The authors declared that no serious complications were observed after a 6-month follow-up and more research is needed to study its efficiency (Özmert and Arslan, 2020). Aghamollaei et al. (2021) assessed the safety of grafting acellular human corneal lenticule seeded with WJ-MSCs in 12 rabbit models. Based on the achievements, the elevated level of keratocyte-specific biomarkers was representative of the capability of WJ-MSCs as keratocyte progenitor cells to reinforce corneal ultrastructure (Aghamollaei et al., 2021). Another study also indicated the differentiation ability of WJ-MSCs into male germ cells using all-trans retinoic acid and Sertoli cell-CM (Dissanayake et al., 2018). The hUC-MSCs also could mitigate spermatogenesis defects induced by paclitaxel and preserve male fertility (Zhang et al., 2023b). It has also been studied that ovine WJ-MSC-CM could play major roles in improving the secondary follicle development and decreasing ROS production following short-term culture (Bezerra MÉ et al., 2019).

In an open-label, single-arm clinical trial registered under ClinicalTrials.gov with the identifier NCT04939337, the efficacy, and safety of locally injected allogeneic hUC-MSCs (TH-SC01), were evaluated in 10 patients with Crohn's disease suffering from complex perianal fistula. The results indicated that six patients achieved combined remission at the 24-week mark. Additionally, the number of draining fistulas decreased in 9 and 7 patients at weeks 12 and 24, respectively. Notably, no serious adverse events were reported. The probability of remaining recurrence-free was determined to be 70% at the 52-week follow-up (Wei et al., 2023a). Moreover, one phase I/II clinical trial has supported the safety and efficacy of two consecutive intracavernous administrations of allogeneic WJ-MSCs in 22 diabetic patients with erectile dysfunction during a 12-month follow-up period (Al Demour et al., 2021).

## 4. Therapeutic application of UC-MSCs and WJ-MSCs derived EVs

EVs derived from UC-MSCs and WJ-MSCs have also demonstrated significant efficiency in the treatment of different disorders (Fig. 2). Exosomes from hUC-MSCs have been shown to considerably enhance osteoblast differentiation in the osteoblast differentiation culture. Additionally, these exosomes have demonstrated specific therapeutic and preventive effects on an OVX animal osteoporosis model. MicroRNA profile in exosomes was shown to be altered by osteogenic differentiation (Yahao and Xinjia, 2021). Zhang et al. (2021) used hyaluronic acid hydrogel (HA-Gel) to encapsulate hUC-MSC-Exosomes and paired them with tailored nanohydroxyapatite/poly-ε-caprolactone (nHP) scaffolds to heal cranial lesions in rats. This composite significantly improved bone regeneration in rats and stimulated the proliferation, migration, and angiogenesis of endothelial progenitor cells. This may be regulated by the signaling axis involving miR-21, NOTCH1, and DLL4 (Zhang et al., 2021). Given the prolonged process of bone regeneration, Yang et al. (2020) developed HA alginate (HA-ALG) cross-linked in situ and embedded with hydroxyapatite (HAP) to effectively retain hUC-MSC-Exosomes at the site of bone defects and they administered the composite to repair bone defects in rats in vivo. Encouragingly, the results demonstrated a significant enhancement in bone regeneration (Yang et al., 2020). It has been indicated that exosomes originating from hUC-MSCs trigger the activation of the AKT signaling pathway, thereby controlling both cell proliferation and osteogenesis (Ren et al., 2022).

In a recent experiment, Chen et al. (2023) found that hWJ-MSC-EVs could reduce IL-1β-induced chondrocyte damage by regulating the

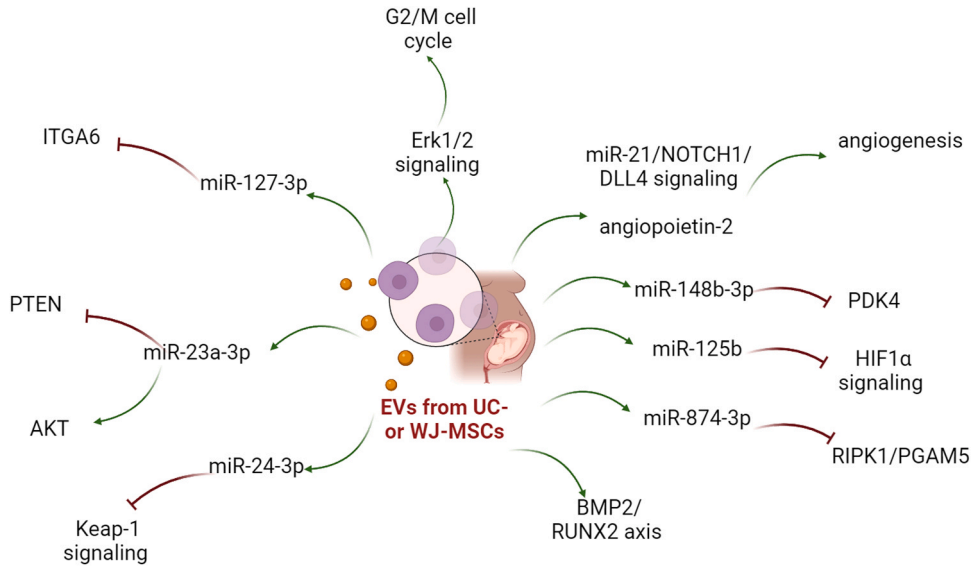


**Fig. 2.** Mesenchymal stem cell-extracellular vesicles derived from Wharton's jelly (WJ-MSC-EVs) or human Umbilical Cord (hUC-MSC-EVs) show therapeutic potential in various diseases by different mechanisms.

BMP2/RUNX2 axis through increased transferrin receptors (Chen et al., 2023a). It has also been discovered that Let-7e-5p, a molecule that is present in WJ-MSC-EVs, has a potential core molecule for enhancing cartilage regeneration by controlling the levels of STAT3 and IGF-1R (Chen et al., 2022). The enhancement of cartilage regeneration was facilitated by hUC-MSC-EVs through the transmission of miR-23a-3p, which acted to inhibit the PTEN level and augment the expression of AKT. In addition, engineered a Gelatin methacrylate/nanoclay hydrogel (Gel-nano) served as a vehicle for the prolonged release of EVs. This hydrogel demonstrated biocompatibility and superior mechanical characteristics. The in vivo studies also revealed that the Gel-nano-EVs loaded with hUC-MSC-EVs effectively stimulated cartilage regeneration in animal models (Hu et al., 2020b). In another study, the use of hUC-MSC-Exosomes was suggested for OA treatment. To enhance the efficacy and duration of therapeutic effects in vivo, the exosomes were modified with membranes containing specially designed chondrocyte-targeting polymers. These engineered exosomes were further enclosed within thiolated hyaluronic acid microgels, creating a "two-phase" releasing system. This innovative approach synergistically contributed to the rejuvenation of aging chondrocytes and facilitated the repair of OA cartilage in a rat model (Cao et al., 2023). The results of a study by Wang et al. (2023) confirmed that hUC-MSCs-Exosomes had a reversed effect of IL-1β on chondrocytes in the expression of collagen type II alpha 1 (COL2A1) and MMP13. The authors confirmed the anti-inflammatory effects of hUC-MSCs-Exosomes in the human articular chondrocytes inflammation model (Wang et al., 2023b). Jiang et al. (2021) have revealed that hWJ-MSC-Exosomes can improve the migration and proliferation of BM-MSCs and chondrocytes in vitro. They also found that exosomes play a potential role in enhancing the effect of the acellular cartilage ECM (ACECM) scaffold and promoting osteochondral regeneration in rabbit and rat knee osteochondral defect repair models through elevating macrophage polarization toward the M2 phenotype and suppressing inflammation. Furthermore, these exosomes could promote cartilage ECM synthesis by exosomal miRNAs (Jiang et al., 2021).

In 2022, a study by Zhu et al. showed that during the healing process, UC-MSC-Exosomes expedited the migration of fibroblasts to the injury site, leading to a notable enhancement in the regeneration of cutaneous nerves in living organisms. Remarkably, UC-MSC-Exo were also observed to facilitate wound closure and skin rejuvenation by attracting fibroblasts, stimulating them to secrete nerve growth factors, and ultimately fostering the regeneration of skin nerves (Zhu et al., 2022). Moreover, UC-MSC-Exosomes expedite the process of cutaneous wound healing by bolstering angiogenesis through the delivery of angiopoietin-2 (Liu et al., 2021b). The findings of another study suggested that hUC-MSC-Exosomes have the potential to alleviate psoriasis-like skin inflammation in mice. This effect is achieved by modulating the expression of IL-23 and IL-17, while also suppressing the maturation and activation of DCs (Zhang et al., 2022b).

As described by Kang et al. (2022), hUC-MSC-Exosomes have been found to alleviate experimental non-alcoholic steatohepatitis through the Nrf2/NQO-1 pathway (Kang et al., 2022). In experimental mouse fibrotic livers, the intravenous injection of hUC-MSC-Exosomes, when carrying BECN1, can also induce ferroptosis in hepatic stellate cells and alleviate liver fibrosis by modulating the xCT/GPX4 axis (Tan et al., 2022). Besides, hUC-MSC-derived exosomal miR-24–3p exhibited hepatoprotective effects by targeting the Keap-1 signaling pathway, suggesting potential therapeutic value for the treatment of non-alcoholic fatty liver disease (Du et al., 2022). WJ-MSC-Exsosomes exhibited a regression of TGF-β-Smad2/3 signaling and a reduction in the expression of fibrotic markers in activated LX-2 cells. However, these effects were significantly enhanced when using e WJ-MSC-Exsosomes pretreated with TGF-β. Hence, exosomes derived from TGFβ-pretreated WJ-MSCs may play a critical role in ameliorating fibrosis and could offer therapeutic benefits for patients with liver fibrosis (Salehipour Bavarsad et al., 2022). Exosomes containing miR-627–5p derived from hUC-MSCs mitigate non-alcoholic fatty liver disease by suppressing the expression of FTO gene (Cheng et al., 2021). Exosomes derived from hWJ-MSCs, enriched with miR-124, stimulated an anti-fibrotic response in an experimental model of liver fibrosis (Niknam et al., 2023).

Moreover, MVs released from hWJ-MSCs ameliorated ischemia-reperfusion (IRI)-induced renal fibrosis by inducing G2/M cell cycle arrest by Erk1/2 signaling (Chen et al., 2017). It has also been indicated that WJ-MSC-EVs inhibited kidney damage by reducing oxidative stress in the early stage of IRI by downregulation of NOX2 and protected the kidney through antioxidation via increasing Nrf2/ARE activation in an animal model (Zhang et al., 2014, 2016). Recently, it was reported by Yu et al. (2023) that exosomes derived from hUC-MSCs containing miR-874–3p were found to target RIPK1/PGAM5, resulting in the alleviation of damage to kidney tubular epithelial cells (Yu et al., 2023). Shi et al. (2023) showed that miR-148b-3p in hUC-MSC-EVs could inhibit apoptosis in kidney I/R injury, protecting against acute kidney injury (AKI). This protective effect is achieved through the downregulation of PDK4 expression, activation of the ATF-6 pathway, and induction of

endoplasmic reticulum (ER) stress (Shi et al., 2023).

Furthermore, Puig-Pijuan and coworkers (2020) showed that WJ-MSCs co-cultured with WJ-MSC-derived EVs could have potential antioxidant and neuroprotective impacts on hippocampal cells (Puig-Pijuan et al., 2020). Bodart-Santos and coworkers (2019) also indicated that EVs derived from WJ-MSCs can preserve hippocampal neurons from oxidative stress and injury induced by amyloid-β oligomers, which was associated with the transfer of enzymatically active catalase contained in them (Bodart-Santos et al., 2019). It has also been revealed that intrathecal transplantation of the WJ-MSC-EVs suppressed inflammation and controlled inflammasome complex activity after SCI in rats (Noori et al., 2021).

A recent finding indicated that administration of MVs derived from hWJ-MSCs enhanced autophagy and ameliorated acute lung injury in rat models by delivery of miR-100 (Chen et al., 2020). In Chen and coworkers study (2019), WJ-MSC-MVs therapy remarkably attenuated bleomycin-induced acute lung injury in a rat model through downregulation of apoptosis and fibrosis and PI3K/AKT/mTOR activation, which was mediated by hepatocyte growth factor (Chen et al., 2019). Another study revealed that through the epigenetic and transcriptomic reprogramming of myeloid cells, EVs from WJ-MSCs rescued the neonatal lung from hyperoxic damage (Willis et al., 2021).

It has also been indicate that the systemic administration of WJ-MSC-EVs, produced on a large scale, enhances cardiac function following myocardial infarction (Bellio et al., 2022b).

In addition, miR-124 from WJ-MSC-derived exosomes decreased proliferation and migration and conferred chemosensitivity in glioblastoma multiform cancer (Sharif et al., 2018). In addition, it has been suggested in an in vitro study that WJ-MSC-EVs-derived miR-125b could prevent triple-negative breast cancer progression by downregulating the HIF1α signaling pathway (Chang et al., 2022). Furthermore, WJ-MSC-Exosomes induced apoptosis and suppressed EMT signaling in cervical cancer cells as an efficient drug carrier system for paclitaxel (Abas et al., 2022). Findings of another study also indicated that miR-127–3p released from hWJ-MSC-EVs played an anti-tumor role via targeting ITGA6, suggesting this as a novel therapeutic approach for choriocarcinoma (Ma et al., 2022). It has also been suggested that hUC-MSC-MVs can trigger cell death mechanisms involving both autophagy and apoptosis in leukemic cell lines (KG-1 cells). These results highlight the considerable anti-proliferative and pro-apoptotic effects of hUC-MSC-MVs on KG-1 cells in an in vitro setting (Khani-Eshratabadi et al., 2023). The lncRNA FAM99B, originating from hUC-MSC-Exosomes, has demonstrated an inhibitory effect on malignant cellular behaviors and tumorigenesis in hepatocellular carcinoma (HCC) which suggest a potential innovative therapeutic approach for the treatment of HCC (Xu et al., 2023). Chen et al. (2023) also reported that hUC-MSC-Exosomes, which carry miR-1827, downregulated SUCNR1, leading to the inhibition of macrophage M2 polarization and ultimately preventing colorectal liver metastasis (Chen et al., 2023b).

Besides, experimental colitis was alleviated by WJ-MSC-EVs treated with thapsigargin (TSG) due to their improved immunomodulatory properties, such as suppression of Th1 and Th17 differentiation and augmentation of Treg and M2-type macrophages (Joo et al., 2021). Another recent study conducted by Wei et al. (2023) revealed that hUC-MSC-Exosomes could alleviate IBD by utilizing miR-129–5p to target ACSL4, thereby inhibiting lipid peroxidation and ferroptosis. This process leads to a reduction in intestinal inflammation and promotes the repair of damage (Wei et al., 2023b).

An in vitro investigation by Crain et al. (2019) illustrated the immunomodulatory effects of canine WJ-MSC-EVs, which suppressed $CD4^+$ T cell proliferation via TGF-β and adenosine signaling (Crain et al., 2019). Another study showed that exosomes from WJ-MSCs ameliorated lymphedema in a murine model, which was associated with the modulation of Ang2 through the Prox1/Akt pathway (Ting et al., 2021). According to a study by Deng et al. (2023), in comparison to the intravenous injection of hUC-MSC-Exosomes, the localized application of a combination of hUC-MSC-Exosomes and GelMA demonstrated greater effectiveness in enhancing endothelial repair in the vein graft and preventing restenosis. This suggests that the suggested biomaterial-based therapeutic strategy holds promise as a treatment for venous graft restenosis (Deng et al., 2023). Findings of another study revealed a significant alleviation of tubal inflammatory infertility resulting from Chlamydia infection in animal models treated with hUC-MSC-EVs by inducing a shift in macrophage polarization from the M1 to the M2 type through the NF-κB signaling pathway. This, in turn, led to an improvement in the local inflammatory microenvironment of the fallopian tubes, ultimately inhibiting tube inflammation (Zhang et al., 2023c).

## 5. Advantages and disadvantages MSC therapy and cell-free therapy using EVs

MSCs can differentiate into a variety of cell types attributable to their multipotent differentiation capability. They have immunomodulatory features that control immunological reactions and lower inflammation. MSCs have the ability to communicate directly with target cells in order to deliver their therapeutic benefits. They release a wide range of cytokines and growth factors to assist in tissue regeneration and repair (Chen et al., 2021). However, there are risks related to cell transplantation, including thrombogenicity, cancer formation, and immunological rejection. Besides, Standardization and scalability issues with MSC production for clinical applications exist, nevertheless (Li et al., 2021b; Coppin et al., 2019).

The therapeutic properties of their parent MSCs, including tissue healing and immunomodulation, are preserved by EVs. The danger of immunological rejection is reduced by EVs since they are non-immunogenic and have minimal immunogenicity. Also, since EV treatment eliminates the dangers of cell engraftment, it offers a safer substitute for cell transplantation. Large-scale production and clinical translation are made easier by the ease of isolating, purifying, and storing EVs (Coppin et al., 2019). Nonetheless, the cargo composition of EVs is still difficult to comprehend and regulate, which causes variation in EV preparations. Ensuring quality control and producing clinical-grade EVs on a large scale present formidable challenges. Moreover, the short half-life of EVs in circulation means that many doses are required to achieve long-lasting therapeutic benefits (Mir and Goettsch, 2020).

When combined, UC-MSCs and EVs have complimentary modes of action that increase their overall therapeutic potential. EVs have the ability to stabilize and shield their cargo from deterioration, which may increase the medicinal compounds' bioavailability and shelf life. By engineering UC-MSCs to manufacture EVs with the required therapeutic cargo, treatment approaches can be customized to the unique demands of individual patients or disease features.

To completely understand the relative effectiveness and long-term results of MSC therapy versus EV therapy in clinical settings, more research is necessary.

## 6. Conclusion and future perspective

In comparison to the adult MSCs, it has been illustrated that UC-MSCs or WJ-MSCs have prominent efficiency in regeneration and treatment of different conditions due to their higher quantity and availability and their easier and noninvasive isolation procedure. These MSCs also pose multipotent differentiation capability and cost-effectiveness along with immuno-privilege and non-tumorigenicity. Besides, the UC-MSCs do not impose any ethical concerns, which makes them an emerging option for various disease therapies.

Several augmenting papers have been published concerning UC-MSCs or their EVs and various diseases including those of the bone, cartilage, nerve, skin, lung, kidney, and liver, as well as sepsis, diabetes, retina, cancer, and autoimmune disorders. UC-MSC therapy with

**Table 14**
The potential role of extracellular vesicles derived from mesenchymal stem cells from umbilical cord or Wharton's jelly in the treatment of various diseases.

| Injury | Study model | Source of EVs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Bone defect | Rat | hUC-MSC-Exosomes/HA-Gel/nHP | - | - | Repaired large bone defects through enhanced angiogenesis, which potentially regulated by the miR-21/NOTCH1/DLL4 signaling axis | (Zhang et al., 2021) |
| Bone defect | Rat | hUC-MSC-Exosomes/ HA-ALG | - | - | Repaired bone defects in rats | (Yang et al., 2020) |
| PMO | Rat | hUC-MSC-Exosomes | Intravenous | 100 μg | Activated the AKT signaling pathway to regulate cell proliferation and osteogenesis | (Ren et al., 2022) |
| Knee OA | In vitro | hWJ-MSC-EVs | - | - | Reduced IL-1β-induced chondrocyte damage by regulating the BMP2/RUNX2 axis through increased transferrin receptors | (Chen et al., 2023a) |
| OA | In vitro | WJ-MSC-EV-derived Let-7e-5p | - | - | Promoted cartilage regeneration by regulating the levels of STAT3 and IGF1R | (Chen et al., 2022) |
| Knee OA | Rat | hUC-MSC- Gel-nano-EV-derived miR-23a-3p | Into the joint | $10 \times 10^8$ particles | Promoted cartilage regeneration by activating PTEN/AKT signaling pathway | (Hu et al., 2020b) |
| OA | Rat | hUC-MSC-Exosomes encapsulated within thiolated hyaluronic acid microgels | - | - | Facilitated the repair of cartilage | (Cao et al., 2023) |
| OA | In vitro | hUC-MSC-Exosomes | - | - | Demonstrated anti-inflammatory effects | (Wang et al., 2023b) |
| Osteochondral defect | In vitro/ rabbit and rat | hWJ-MSC-Exosomes/ ACECM scaffold | Intra-articular | 25 μg/mL | Promoted osteochondral regeneration via inhibition of joint cavity inflammation by Exos and the promotion of cartilage ECM synthesis by exosomal miRNAs | (Jiang et al., 2021) |
| Cutaneous damage | Mice | UC-MSC-Exosomes | - | 100 μg | Promoted skin and nerve regeneration | (Zhu et al., 2022) |
| Cutaneous wound | Rat | hUC-MSC-Exosomes | - | - | Accelerated wound healing by enhancing angiogenesis through delivering angiopoietin-2 | (Liu et al., 2021b) |
| Psoriasis-like Skin Inflammation | Mice | hUC-MSC-Exosomes | - | - | Ameliorated psoriasis-like skin inflammation in mice by regulating the expression of IL-23 and IL-17, and inhibiting the maturation and activation of DCs | (Zhang et al., 2022b) |
| Non-alcoholic steatohepatitis | Mice | hUC-MSC-Exosomes | Intravenous | - | Ameliorated hepatitis via Nrf2/NQO-1 pathway | (Kang et al., 2022) |
| Liver fibrosis | Mice | hUC-MSC-Exosomes delivering BECN1 | Intravenous | - | 1 induces ferroptosis of HSCs via regulating the xCT/GPX4 axis | (Tan et al., 2022) |
| Non-alcohol fatty liver | Mice | hUC-MSC-Exosomal miR-24–3p | - | - | Ameliorated liver disease by targeting Keap-1 | (Du et al., 2022) |
| Non- alcoholic fatty liver disease | Rat | hUC-MSC-Exosomal miR-627–5p | - | - | Ameliorated liver disease by repressing FTO expression | (Cheng et al., 2021) |
| Liver fibrosis | Mice | hWJ-MSC-Exosomal miR-124–3p | - | - | Promoted anti-fibrotic response | (Niknam et al., 2023) |
| Renal IRI | Rat | hWJ-MSC-MVs | Intravenous | - | Ameliorated IRI fibrosis by releasing from G2/M cell cycle arrest | (Chen et al., 2017) |
| Renal IRI | Rat | hWJ-MSC-MVs | Intravenous | - | Alleviated the oxidative stress in the early stage of kidney IRI through suppressing NOX2 expression | (Zhang et al., 2014) |
| AKI | Rat | hWJ-MSC-EVs | Intravenous | - | Protected kidney through anti-oxidation by enhancing Nrf2/ARE activation | (Zhang et al., 2016) |
| Kidney damage | Mice | hUC-MSC-Exosomal miR-874–3p | - | - | Regulated necroptosis through miR-874–3p to attenuate renal tubular epithelial cell injury and enhanced repair | (Yu et al., 2023) |
| Renal IRI | Mice | hUC-MSC-EVs loaded with miR-148b-3p | Intravenous | $5 \times 10^{10}$ particles | Inhibited apoptosis in kidney injury and downregulated PDK4 expression, activated ATF-6 pathway, and induced ER stress | (Shi et al., 2023) |
| AD | In vitro | hWJ-MSC-EVs | - | - | Protected hippocampal neurons from oxidative stress and synapse damage induced by amyloid-β oligomers | (Bodart-Santos et al., 2019) |
| SCI | Rat | WJ-MSC-EVs | Intrathecal | - | Suppressed inflammation and controlled inflammasome complex activity | (Noori et al., 2021) |
| ALI | Rat | hWJ-MSC-MV-miR-100 | Intratracheal | $1 \times 10^6$ cells | Enhanceed autophagy and ameliorated acute lung injury | (Chen et al., 2020) |
| ALI | Rat | hWJ-MSC-MVs | - | - | Inhibited apoptosis and fibrosis in lung tissues and PI3K/AKT/mTOR activation which was partly mediated through HGF mRNA. | (Chen et al., 2019) |
| Glioblastoma multiform cancer | In vitro | hWJ-MSC-exosomal miR-124 | - | - | Decreased Cell Proliferation and Migration, and Confers Chemosensitivity | (Sharif et al., 2018) |
| TNBC | In vitro/ mice | hWJ-MSC-EVs-derived miR-125b | Intravenous | 10 μg | Inhibited the tumor environment via the HIF1α signaling pathway | (Chang et al., 2022) |
| Cervical cancer | In vitro | hWJ-MSC-Exosomes | - | - | Induced apoptosis and suppress EMT signaling | (Abas et al., 2022) |
| Choriocarcinoma | In vitro | hUC-MSC- EV-derived miR-127–3p | - | - | Exhibited anti-tumor effects by targeting ITGA6 | (Ma et al., 2022) |
| AML | In vitro | hUC-MSC- MVs | - | - | Induced cell death pathways of autophagy and apoptosis in the KG-1 cell lines and exerted potent antiproliferative and proapoptotic effects on KG-1 cells in vitro. | (Khani-Eshratabadi et al., 2023) |

(*continued on next page*)

**Table 14** (*continued*)

| Injury | Study model | Source of EVs | Infusion method | Dose of injection | Outcome | Reference |
|---|---|---|---|---|---|---|
| Hepatocellular Carcinoma | In vitro | hUC-MSC- exosomal lncRNA FAM99B | - | - | Inhibited malignant cellular phenotypes and tumorigenesis | (Xu et al., 2023) |
| Colorectal cancer | In vitro/ mice | hUC-MSC- exosomal miR-1827 | - | - | Inhibited M2 macrophage polarization by downregulating SUCNR1 expression, and inhibited proliferating, migrating and invading properties of CRC cells | (Chen et al., 2023b) |
| IBD | Mice | Thapsigargin-Treated-hWJ-MSC-EVs | Intraperitoneal | 200 μg | Ameliorated colitis via enhancing immunomodulatory properties | (Joo et al., 2021) |
| IBD | Mice | hUC-MSC-exosomal mir-129–5p | Intravenous | 1 mg | Relieved IBD by targeting ACSL4 to inhibit lipid peroxidation and ferroptosis, reducing intestinal inflammation and repairing damages | (Wei et al., 2023b) |

PMO: postmenopausal osteoporosis; OA: osteoarthritis; AKI: acute kidney injury; IRI: ischemia-reperfusion; AD: Alzheimer's disease; SCI: spinal cord injury; ALI: acute lung injury; TNBC: triple negative breast cancer; AML: acute myeloid leukemia; IBD: inflammatory bowel disease

modification, such as combination with scaffold, miRNA loading, target protein-overexpression, and target factor-primed MSCs can significantly promote their therapeutic effects. EVs can also propose a safer and emerging choice for the treatment of disorders, which is associated with their lower tumorigenic and immunogenic features as well as anti-inflammatory properties than their parental MSCs.

However, despite the promising outcomes, ensuring quality control and reproducibility of batches of UC-MSCs and their associated EVs for clinical application in treating various disorders, presents significant challenges. These obstacles encompass optimizing the administration route and dosage of UC-MSCs and EVs, as well as determining the ideal timing for treatment of different disorders. Moreover, variations in isolation techniques affect the reliability of functional assessments, leading to inconsistent yields and purity of EV preparations. Furthermore, the absence of standardized functional assays poses a notable barrier to comparing findings across various studies. Additionally, meeting the demands of clinical settings necessitates critical optimization of culture conditions, expansion protocols, and cryopreservation techniques. A persistent challenge also involves thoroughly evaluating the long-term safety and effectiveness of MSCs and EVs in clinical contexts.

It is true that one of the most important factors in boosting the effectiveness of these treatments is to improve MSC and EV migration and circulation to the target locations. To overcome this obstacle, a number of approaches can be investigated. The homing capacity of UC-MSCs or their EVs can be improved by altering their surface with ligands that precisely target receptors expressed on cells at the target region. Targeted distribution can also be facilitated by attaching molecules like antibodies or peptides that recognize receptors that are overexpressed in injured tissues. To drive MSCs or EVs toward particular tissues or organs, homing signals can be incorporated into them through genetic engineering methods. This may entail the overexpression of adhesion molecules or chemokine receptors, which facilitate migration to specific sites. Moreover, it is possible to increase the migration and circulation of MSC or EV treatment to target regions in a synergistic manner by combining them with additional techniques, such as pharmacological agents, like growth factors or chemokines, or physical techniques, like magnetic guiding or ultrasound. Additionally, increasing the effectiveness of EVs by engineering them to express surface proteins or peptides can facilitate targeting and uptake by particular cell types. Moreover, EVs can be made more functional and trackable by adding medicinal cargo. Besides, the homing of MSCs or EVs to desired areas can be enhanced by selecting suitable methods of administration, such as intravenous, intra-arterial, or intranasal delivery, depending on the target tissue.

Nevertheless, more clinical research is obligatory to warrant their safety and effectiveness before application in the clinic. Moreover, comprehensive research of the mechanisms involved in EV biogenesis, pharmacokinetics, and biodistribution is needed to be achieved. Establishing robust protocols, implementing good manufacturing practices (GMP) guidelines, and implementing rigorous quality control measures are critical steps toward addressing these challenges and advancing the clinical translation of EV-based therapies. In addition, more effort is required to understand the mechanisms through which the beneficial properties of UC-MSCs are extended and therefore facilitate their modification to progress future clinical use.

## Ethics approval and consent to participate

Not applicable.

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## CRediT authorship contribution statement

**Fuzail Ahmad:** Writing – review & editing, Validation. **Haroonrashid M. Hattiwale:** Validation, Supervision, Funding acquisition. **Mohammad Azhar Kamal:** Validation, Software, Conceptualization. **Ayyub Ali Patel:** Writing – original draft, Validation, Conceptualization. **Asma'a H. Mohamed:** Validation, Supervision, Conceptualization. **Jasur Rizaev:** Writing – original draft, Writing – review & editing. **Waleed Al Abdulmonem:** Writing – review & editing, Validation, Investigation. **Azfar Jamal:** Writing – review & editing, Validation, Investigation. **Ayaz Khurram Mallick:** Writing – review & editing, Validation. **Maytham T. Qasim:** Writing – original draft, Validation, Data curation.

## Data Availability

No data was used for the research described in the article.

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### *Consent for publication*

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### *Competing interests*

The authors declare that they have no competing interests.

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