

Review Article

Wharton's Jelly Mesenchymal Stem Cell Therapy for Skin Wound Healing

Ana I García-Guillén^{1#}, José E Millán-Rivero^{1,2#}, Carlos M Martínez³, Jose M Moraleda^{1,2} and David García-Bernal^{1,2*}

¹Hematopoietic Transplant and Cellular Therapy Unit, Instituto Murciano de Investigación Biosanitaria IMIB-Arixaca, Murcia, Spain

²Department of Internal Medicine, Medicine School, University of Murcia, Spain

³Experimental Pathology Unit, Instituto Murciano de Investigación Biosanitaria IMIB-Arixaca, Murcia, Spain

*Equal contribution

Abstract

The management of chronic wounds still remains an important unsolved problem in clinical practice. Different therapeutic approaches, including regenerative medicine or tissue engineering strategies, have been used to ameliorate this pathology to achieve skin regeneration. Mesenchymal stem cells represent a potential therapeutic option for chronic wounds due to their differentiation, proliferation, and immunomodulatory properties. Among them, Wharton's jelly mesenchymal stem cells from the umbilical cord are a type of extraembryonic stem cells that have been proven to be very effective for treating chronic wounds. These cells possess some advantages when compared to adult mesenchymal stem cells such as higher proliferation rate, multipotency, and low immunogenicity. They act as potent immunomodulators during the inflammation phase of wound healing and are also involved in replacing the damaged skin tissue. In this review we will discuss the findings obtained in different preclinical and clinical studies performed with Wharton's jelly mesenchymal stem cells systemically administered, implanted on a biocompatible

scaffold, or using mesenchymal stem cell-derived extracellular vesicles or their conditioned medium as possible treatments for chronic wounds

Keywords: Chronic wounds; Mesenchymal stem cells; Wharton's jelly; Wound healing

Introduction

The skin is one of the most important protective organs in humans. When the skin is injured a wound healing process starts in order to regenerate the normal structure of skin and adnexal appendages. When the damage is too extensive or there is an alteration of the regenerative process, the healing process can progress to develop chronic wounds or leading the induction of a fibrotic response which induce scar formation and loss of skin adnexal, a major problem in some kind of pathologies (i.e., extensive burns).

Chronic wound healing represents a major public health issue [1], especially when patients have other underlying diseases. Some chronic wound treatments pursue to control the causative factors, but those based on the use of skin substitutes have been suggested as the most effective choices [2].

Actually, stem cell-based therapy is an effective alternative to treat skin diseases because of their regenerative potential [3-6]. The ability of Mesenchymal Stem Cells (MSCs) to mediate tissue regeneration through different mechanisms such as transdifferentiation into multiple skin cell types, mesenchymal-epithelial transition, direct cell-to-cell contacts, production of extracellular vesicles, and secretion of a large number of soluble molecules (i.e., chemokines, cytokines, growth factors, and extracellular matrix components) make them useful in the treatment of many pathological skin conditions [7-12]. MSCs can be isolated from different sources, both adult and fetal tissues. The fetal MSCs come from tissues such as the placenta, amniotic membrane, amniotic fluid and Wharton's jelly from the umbilical cord stroma (Wj-MSCs) [13]. Among them, Wj-MSCs present some advantages compared to adult MSCs because they retain characteristics of embryonic stem cells such as higher expression of pluripotency markers including Nanog, Oct4, Sox2 and c-Kit [14]. The use of these fetal MSCs does not have ethical concerns because they come from extraembryonic tissues that are discarded after birth. In addition, they are obtained without using invasive procedures, and they present a greater multipotentiality, better proliferative rate and lower capacity to form teratomas upon transplantation as compared to adult bone marrow or adipose tissue-derived MSCs [15-21]. Furthermore, some fetal MSCs, mainly the Wj-MSCs, have demonstrated less immunogenicity and better immunomodulatory properties than their adult's counterparts by secreting a significant number of anti-inflammatory molecules such as TGF β , IDO, IL-10, PGE₂ and TSG-6 [22,23]. Many studies, most of them preclinical, show the advantages of the employment of adult and fetal MSCs for the treatment of several diseases; however, more mechanistic studies are needed to translate this therapeutic tool to a clinical phase [8,19,24-28].

***Corresponding author:** David García-Bernal, Hematopoietic Transplant and Cellular Therapy Unit, Instituto Murciano de Investigación Biosanitaria Virgen de la Arrixaca and Internal Medicine Department, Medicine School, University of Murcia, Avenida Buenavista s/n. El Palmar, Murcia, Spain, Tel: +34 868888497; Fax: +34 868884150; E-mail: david.garcia23@um.es

Citation: García-Guillén AI, Millán-Rivero JE, Martínez CM, Moraleda JM, García-Bernal D (2020) Wharton's Jelly Mesenchymal Stem Cell Therapy for Skin Wound Healing. J Stem Cell Res Dev Ther 6: 037.

Received: May 11, 2020; **Accepted:** May 20, 2020; **Published:** May 28, 2020

Copyright: © 2020 García-Guillén AI, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

In this review, we will summarize some of the most relevant findings obtained in this research area.

Wound Healing

The skin is the largest structure of the organism and acts as a barrier, regulating water and electrolyte balance, and protecting the organism from microbes and other harmful external agents [29]. When the integrity of the skin is disrupted, a cutaneous wound appears [1]. The wound healing is a complex process and consists of three different sequential and overlapping stages: the inflammatory phase, proliferative phase (i.e., neoangiogenesis, granulation tissue formation, and re-epithelization), and the extracellular matrix remodeling phase. In all these stages, different soluble mediators and blood cells, extracellular matrix components, and parenchyma cells are involved [1,30].

This progression may be sometimes disrupted due to the presence of underlying comorbidities or other secondary factors such as neuropathies, vasculitis, or extensive burns. All of them can cause the loss or delay of the restitution and integument progression of the skin and induce the appearance of a chronic, non-healing wound [1,31], and keloids or scars instead of healthy skin [32]. Additionally, this situation may get worse with the appearance of opportunistic infections which aggravate the progression of these pathologies [33].

To date, there are only partial remedies for this condition, and it is an unmet clinical need to develop new therapeutic strategies to avoid a state of chronic, non-healing wounds and to promote proper skin re-epithelization.

Mesenchymal Stem Cells

MSCs are defined as undifferentiated cells with self-renew potential and the capacity to differentiate into various cell types [34], following the minimum criteria established by the International Society for Cellular Therapy [35]: 1) MSCs must possess plastic adherence in culture conditions; 2) 95% of the cells must express the markers CD105 (endoglin), CD73 (ecto-5'-nucleotidase) and CD90 (Thy1), and no more than 2% of the cells must be positive for CD45 (pan-leukocyte marker), CD34 (hematopoietic and endothelial progenitor cells marker), CD14 or CD11b (expressed on macrophages and monocytes), CD79a or CD19 (B cells markers) and HLA class II; and 3) they must be able to differentiate in culture into osteoblasts, adipocytes, and chondroblasts under specific differentiating conditions.

MSCs possess potent immunomodulatory properties since they can inhibit the proliferation and function of different immune cells such as CD4⁺ and CD8⁺ T lymphocytes, B lymphocytes, Dendritic Cells (DC), or natural killer (NK) cells [36-40]; and they also can reduce immune cell cytokine secretion [41]. MSCs are involved in the macrophages phenotype switch (from pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype) [42], and stimulate T lymphocytes to change into an anti-inflammatory Th2 phenotype [43]. Furthermore, MSCs can induce immunomodulatory effects by secretion of various anti-inflammatory cytokines such as TGFβ, IDO, PGE₂, nitric oxide, IL-6, semaphorin-3A, or galectins Gal-1 and Gal-9 [44-50].

A variety of studies have demonstrated that MSCs migrate to inflamed tissues following signals such as growth factors, cytokines, and chemokines. Also MSCs display paracrine mechanisms of action in the tissues, and some of their beneficial effects seem to be mediated

by the secretion of trophic factors (e.g., VEGF, angiopoietin, FGF, CNTF, GDNF, HGF and IGF) [51]. Secreted bioactive factors can stimulate the regeneration and repair of injured tissues by inducing migration and proliferation of circulating stem cells and other resident tissue-specific cells [52], can present immunomodulatory effects in the site of action and/or present anti-apoptotic and pro-angiogenic capacity [53]. Importantly, some studies have indicated that in wound healing MSCs increase the response of many cell types in the wound area including epithelial cells, endothelial cells, keratinocytes and fibroblasts as a result of their trophic-mediated effects [54].

Wound Healing and Wj-MSc Treatment

The role of MSCs in the treatment of chronic wound and non-healing ulcers has been demonstrated in both preclinical and clinical studies as a strategy to repair and restore the function of the skin [2,3,55-57]. Treatments with MSCs have resulted in clinical improvement of chronic wounds in some patients and mice, accelerating the time of reepithelization of the wound without scarring [58,59].

In some studies, MSCs were administered intravenously or delivered on a biocompatible scaffold, showing no signs of immune rejection, skin retraction, or scar formation [59-64]. The delivery of the MSCs on a biological scaffold seems to have some benefits compared to systemic administration or locally implanted around the wound [65,66], since these routes of administration limit the engraftment and the survival of the cells. The use of a scaffold provides cell support and chemical and structural signals that help MSCs in their regenerative or reparative role in the wound [67]. It was demonstrated that the employment of Wj-MSCs in combination with decellularized amniotic membrane as scaffold showed better results than the direct injection of Wj-MSCs, with less formation of scars, and better regeneration of the skin [17,68]. Other studies combined the use of Wj-MSCs-laden collagen scaffolds with hyperbaric oxygen therapy resulting in improved wound healing progression in diabetic mice [69]. Recent work by our group showed that the administration of Wj-MSCs on a silk fibroin scaffold on the wound beds promoted a decrease of the inflammatory infiltrates, diminished fibrotic progression, improved neoangiogenesis, and accelerated skin regeneration [60].

Apart from direct intercellular interactions within the tissues, MSCs can exert part of their pivotal trophic and immunomodulatory function by secretion of a large number of soluble molecules. Thus, some researchers have used the Wj-MSc-conditioned medium, which contains all of these factors, for the prevention and treatment of skin ulcers. Some studies showed that the use of this conditioned medium was able to accelerate wound closure and enhance the wound healing process [70,71].

On the other hand, Extracellular Vesicles (EVs) (i.e., microvesicles, exosomes, and apoptotic bodies) are lipid bilayer particles containing mRNAs, microRNAs, lipids and proteins released by cells that can interact with neighbouring cells and influence their behaviour [72]. The potential role of the MSC-derived Extracellular Vesicles (EVs) in the wound healing process has also been investigated. Preliminary results showed that EVs have also displayed angiogenic, immunomodulatory, and immunosuppressive activity. These important properties make them a useful therapeutic approach, also in wound healing [12]. Some recent findings showed that Wj-derived EVs were also able to stimulate the wound healing process [73,74]. Wj-MSc-mediated effects on wound healing, or by their related cellular products (i.e., conditioned medium or EVs) are summarized in table 1.

Cell-based therapy	Effects on wound healing	References
Only Wj-MSCs	Accelerate formation of the epithelial sheet	[60]
	Increase wound contraction and improve epithelization, neovascularization and collagen characteristics	[61]
	Accelerate wound closure by enhancing collagen deposition and angiogenesis	[62]
	Stimulate higher re-epithelization and newly formed capillary vessels in the skin wounds	[64]
Wj-MSCs combined with biocompatible scaffolds	Reduce scar formation with hair growth and improve biomechanical properties of regenerated skin	[17]
	Induce formation of well-organized and vascularized granulation tissue, enhance re-epithelization, and reduce formation of fibrotic scar tissue	[60]
	Induced a faster healing and a higher number of blood vessels in the wound	[63]
	Decrease wound healing time and wound size in chronic diabetic wounds	[68]
	Accelerate healing effect in chronic diabetic wounds	[69]
Wj-MSCs-derived conditioned medium	Enhances normal skin fibroblast proliferation and migration, and stimulate wound healing	[66]
	Regenerates sebaceous glands and angiogenesis, without scar formation	[70]
	Enhances re-epithelization, increases angiogenesis and stimulates sebaceous gland and hair follicle formation	[71]
Wj-MSCs-derived extracellular vesicles	Produce higher collagen deposition and stimulate wound healing	[68]
	Attenuated full-thickness skin wounding by enhancing epidermal re-epithelialization and dermal angiogenesis	[74]

Table 1: Summary of therapeutic effects of Wj-MSCs in skin wound healing.

Due to the large number of preclinical studies carried out to study the therapeutic effect of Wj-MSCs on wound healing, and the mostly beneficial results obtained, different clinical trials have been recently implemented in order to study the safety and therapeutic efficacy of Wj-MSCs for the treatment of acute burns (ClinicalTrials.gov Identifiers: NCT01443689 and NCT03237442), large area skin lesions (NCT02669199 and NCT02672280), and chronic diabetic foot ulcers (NCT04104451).

Conclusion

The choice of Wj-MSCs as the therapeutic option for wound healing has been demonstrated as a suitable cell therapy alternative to stimulate skin repair. There are many experimental studies showing the anti-inflammatory, immunomodulatory and regenerative/reparative properties of Wj-MSCs. Although more preclinical and clinical research is necessary to optimize the route of administration, dose, or the best way to deliver the cells into the wound, with or without scaffold, Wj-MSC and their related cellular products (i.e., conditioned medium or EVs) seem to be a really compelling strategy for the treatment of ulcers and chronic, non-healing wounds in the clinical practice.

Funding

This work was supported by Instituto de Salud Carlos III (IS-CIII) and the Spanish Network of Cell Therapy (TerCel), RETICS subprogram of the I+D+I 2013-2016 Spanish National Plan, project “RD16/0011/0001” funded by ISCIII and co-founded by European Regional Development Funds “una manera de hacer Europa”.

Competing Interest

The authors declare that they have no competing interests.

References

- Kirby GT, Mills SJ, Cowin AJ, Smith LE (2015) Stem Cells for Cutaneous Wound Healing. *Biomed Res Int* 2015: 285869.
- Isakson M, de Blacam C, Whelan D, McArdle A, Clover AJ (2015) Mesenchymal Stem Cells and Cutaneous Wound Healing: Current Evidence and Future Potential. *Stem cells international* 2015: 831095.
- Castellanos G, Bernabe-Garcia A, Moraleda JM, Nicolas FJ (2017) Amniotic membrane application for the healing of chronic wounds and ulcers. *Placenta* 59: 146-153.
- Insausti CL, Alcaraz A, Garcia-Vizcaino EM, Mrowiec A, Lopez-Martinez MC, et al. (2010) Amniotic membrane induces epithelialization in massive posttraumatic wounds. *Wound Repair Regen* 18: 368-377.
- Caplan AI (2007) Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *Journal of cellular physiology* 213: 341-347.
- Dimarino AM, Caplan AI, Bonfield TL (2013) Mesenchymal stem cells in tissue repair. *Frontiers in immunology* 4: 201.
- Sasaki M, Abe R, Fujita Y, Ando S, Inokuma D, et al. (2008) Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. *J Immunol*, 180: 2581-2587.
- Millan-Rivero JE, Nadal-Nicolas FM, Garcia-Bernal D, Sobrado-Calvo P, Blanquer M, et al. (2018) Human Wharton's jelly mesenchymal stem cells protect axotomized rat retinal ganglion cells via secretion of anti-inflammatory and neurotrophic factors. *Scientific reports* 8: 16299.
- Leuning DG, Beijer NRM, du Fosse NA, Vermeulen S, Lievers E, et al. (2018) The cytokine secretion profile of mesenchymal stromal cells is determined by surface structure of the microenvironment. *Scientific reports* 8: 7716.
- Linard C, Brachet M, Strup-Perrot C, L'Homme B, Busson E, et al. (2018) Autologous Bone Marrow Mesenchymal Stem Cells Improve the Quality and Stability of Vascularized Flap Surgery of Irradiated Skin in Pigs. *Stem cells translational medicine* 7: 569-582.
- Zou Z, Zhang Y, Hao L, Wang F, Liu D, et al. (2010) More insight into mesenchymal stem cells and their effects inside the body. *Expert opinion on biological therapy* 10: 215-230.
- Casado-Diaz A, Quesada-Gomez JM, Dorado G (2020) Extracellular Vesicles Derived From Mesenchymal Stem Cells (MSC) in Regenerative Medicine: Applications in Skin Wound Healing. *Frontiers in bioengineering and biotechnology* 8: 146.
- Haddad R, Saldanha-Araujo F (2014) Mechanisms of T-cell immunosuppression by mesenchymal stromal cells: what do we know so far? *BioMed research international* 2014: 216806.
- Fong CY, Chak LL, Biswas A, Tan JH, Gauthaman K, et al. (2011) Human Wharton's jelly stem cells have unique transcriptome profiles compared to human embryonic stem cells and other mesenchymal stem cells. *Stem cell reviews and reports* 7: 1-16.

15. Abdulrazzak H, Moschidou D, Jones G, Guillot PV (2010) Biological characteristics of stem cells from foetal, cord blood and extraembryonic tissues. *J R Soc Interface* 6: 689-706.
16. Marcus AJ, Woodbury D (2008) Fetal stem cells from extra-embryonic tissues: do not discard. *Journal of cellular and molecular medicine* 12: 730-742.
17. Sabapathy V, Sundaram B, V MS, Mankuzhy P, Kumar S (2014) Human Wharton's Jelly Mesenchymal Stem Cells plasticity augments scar-free skin wound healing with hair growth. *PLoS One* 9: 93726.
18. La Rocca G, Anzalone R, Corrao S, Magno F, Loria T, et al. (2009) Isolation and characterization of Oct-4+/HLA-G+ mesenchymal stem cells from human umbilical cord matrix: differentiation potential and detection of new markers. *Histochemistry and cell biology* 131: 267-282.
19. Weiss ML, Medicetty S, Bledsoe AR, Rachakatla RS, Choi M, et al. (2006) Human umbilical cord matrix stem cells: preliminary characterization and effect of transplantation in a rodent model of Parkinson's disease. *Stem Cells* 24: 781-792.
20. Kern S, Eichler H, Stoeve J, Kluter H, Bieback K (2006) Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells* 24: 1294-1301.
21. Gauthaman K, Fong CY, Suganya CA, Subramanian A, Biswas A, et al. (2012) Extra-embryonic human Wharton's jelly stem cells do not induce tumorigenesis, unlike human embryonic stem cells. *Reprod Biomed Online* 24: 235-246.
22. Prasanna SJ, Gopalakrishnan D, Shankar SR, Vasandan AB (2010) Pro-inflammatory cytokines, IFN γ and TNF α , influence immune properties of human bone marrow and Wharton jelly mesenchymal stem cells differentially. *PLoS One* 5: 9016.
23. Deuse T, Stubbendorff M, Tang-Quan K, Phillips N, Kay MA, et al. (2011) Immunogenicity and immunomodulatory properties of umbilical cord lining mesenchymal stem cells. *Cell transplant* 20: 655-667.
24. Mitchell KE, Weiss ML, Mitchell BM, Martin P, Davis D, et al. (2003) Matrix cells from Wharton's jelly form neurons and glia. *Stem Cells* 21: 50-60.
25. Wu KH, Zhou B, Yu CT, Cui B, Lu SH, et al. (2007) Therapeutic potential of human umbilical cord derived stem cells in a rat myocardial infarction model. *Ann Thorac Surg* 83: 1491-1498.
26. Moodley Y, Atienza D, Manuelpillai U, Samuel CS, Tchongue J, et al. (2009) Human umbilical cord mesenchymal stem cells reduce fibrosis of bleomycin-induced lung injury. *Am J Pathol* 175: 303-313.
27. Gao LR, Zhang NK, Zhang Y, Chen Y, Wang L, et al. (2018) Overexpression of apelin in Wharton's jelly mesenchymal stem cell reverses insulin resistance and promotes pancreatic beta cell proliferation in type 2 diabetic rats. *Stem Cell Res Ther* 9: 339.
28. Lund RD, Wang S, Lu B, Girman S, Holmes T, et al. (2007) Cells isolated from umbilical cord tissue rescue photoreceptors and visual functions in a rodent model of retinal disease. *Stem Cells* 25: 602-611.
29. Singer AJ, Clark RA (1999) Cutaneous wound healing. *N Engl J Med* 341: 738-746.
30. Coutinho P, Qiu C, Frank S, Tamber K, Becker D (2003) Dynamic changes in connexin expression correlate with key events in the wound healing process. *Cell Biol Int* 27: 525-541.
31. Guo S, Dipietro LA (2010) Factors affecting wound healing. *J Dent Res* 89: 219-229.
32. Kose O, Waseem A (2008) Keloids and Hypertrophic Scars: Are They Two Different Sides of the Same Coin? *Dermatol Surg* 34: 336-346.
33. Baron JM, Glatz M, Proksch E (2020) Optimal Support of Wound Healing: New Insights. *Dermatology*, Pg no: 1-8.
34. Owen M, Friedenstein AJ (1988) Stromal stem cells: marrow-derived osteogenic precursors. *Ciba Found Symp* 136: 42-60.
35. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, et al. (2006) Minimal Criteria for Defining Multipotent Mesenchymal Stromal Cells. The International Society for Cellular Therapy Position Statement. *Cytotherapy* 8: 315-317.
36. Di Nicola M, Carlo-Stella C, Magni M, Milanese M, Longoni PD, et al. (2002) Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood* 99: 3838-3843.
37. Asari S, Itakura S, Ferreri K, Liu CP, Kuroda Y, et al. (2009) Mesenchymal stem cells suppress B-cell terminal differentiation. *Exp Hematol* 37: 604-615.
38. Jiang XX, Zhang Y, Liu B, Zhang SX, Wu Y, et al. (2005) Human Mesenchymal Stem Cells Inhibit Differentiation and Function of Monocyte-Derived Dendritic Cells. *Blood* 105: 4120-4126.
39. Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, et al. (2007) Mesenchymal Stem Cells Inhibit Dendritic Cell Differentiation and Function by Preventing Entry Into the Cell Cycle. *Transplantation* 83: 71-76.
40. Valencia J, Blanco B, Yanez R, Vazquez M, Herrero Sanchez C, et al. (2016) Comparative Analysis of the Immunomodulatory Capacities of Human Bone Marrow- And Adipose Tissue-Derived Mesenchymal Stromal Cells From the Same Donor. *Cytotherapy* 18: 1297-1311.
41. Zhou C, Yang B, Tian Y, Jiao H, Zheng W, et al. (2011) Immunomodulatory effect of human umbilical cord Wharton's jelly-derived mesenchymal stem cells on lymphocytes. *Cell Immunol* 272: 33-38.
42. Ylostalo JH, Bartosh TJ, Coble K, Prockop DJ (2012) Human mesenchymal stem/stromal cells cultured as spheroids are self-activated to produce prostaglandin E2 that directs stimulated macrophages into an anti-inflammatory phenotype. *Stem Cells* 30: 2283-2296.
43. Ghannam S, Pene J, Moquet-Torcy G, Jorgensen C, Yssel H (2010) Mesenchymal stem cells inhibit human Th17 cell differentiation and function and induce a T regulatory cell phenotype. *J Immunol* 185: 302-312.
44. Nauta AJ, Fibbe WE (2007) Immunomodulatory properties of mesenchymal stromal cells. *Blood* 110: 3499-3506.
45. English K (2013) Mechanisms of mesenchymal stromal cell immunomodulation. *Immunol Cell Biol* 91: 19-26.
46. Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, et al. (2006) Role for interferon-gamma in the immunomodulatory activity of human bone marrow mesenchymal stem cells. *Stem Cells* 24: 386-398.
47. Waterman RS, Tomchuck SL, Henkle SL, Betancourt AM (2010) A new Mesenchymal Stem Cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an Immunosuppressive MSC2 phenotype. *PLoS One* 5: 10088.
48. Opitz CA, Litztenburger UM, Lutz C, Lanz TV, Tritschler I, et al. (2009) Toll-like receptor engagement enhances the immunosuppressive properties of human bone marrow-derived mesenchymal stem cells by inducing indoleamine-2,3-dioxygenase-1 via interferon-beta and protein kinase R. *Stem Cells* 27: 909-919.
49. Ge W, Jiang J, Arp J, Liu W, Garcia B, et al. (2010) Regulatory T-cell generation and kidney allograft tolerance induced by mesenchymal stem cells associated with indoleamine 2,3-dioxygenase expression. *Transplantation* 90: 1312-1320.
50. Harris SG, Padilla J, Koumas L, Ray D, Phipps RP (2002) Prostaglandins as modulators of immunity. *Trends Immunol* 23: 144-150.
51. Chen L, Tredget EE, Wu PY, Wu Y (2008) Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. *PLoS One* 3: 1886.

52. Gnecci M, Zhang Z, Ni A, Dzau VJ (2008) Paracrine mechanisms in adult stem cell signaling and therapy. *Circ Res* 103: 1204-1219.
53. Fu Y, Karbaat L, Wu L, Leijten J, Both SK, et al. (2017) Trophic Effects of Mesenchymal Stem Cells in Tissue Regeneration. *Tissue Eng Part B Rev* 23: 515-528.
54. Hocking AM, Gibran NS (2010) Mesenchymal stem cells: paracrine signaling and differentiation during cutaneous wound repair. *Exp Cell Res* 316: 2213-2219.
55. Dash NR, Dash SN, Routray P, Mohapatra S, Mohapatra PC (2009) Targeting nonhealing ulcers of lower extremity in human through autologous bone marrow-derived mesenchymal stem cells. *Rejuvenation Res* 12: 359-366.
56. Lu D, Chen B, Liang Z, Deng W, Jiang Y, et al. (2011) Comparison of bone marrow mesenchymal stem cells with bone marrow-derived mononuclear cells for treatment of diabetic critical limb ischemia and foot ulcer: a double-blind, randomized, controlled trial. *Diabetes Res Clin Pract* 92: 26-36.
57. Valiente MR, Nicolas FJ, Garcia-Hernandez AM, Fuente Mora C, Blanquer M, et al. (2018) Cryopreserved amniotic membrane in the treatment of diabetic foot ulcers: a case series. *J Wound Care* 27: 806-815.
58. Badiavas EV, Falanga V (2003) Treatment of chronic wounds with bone marrow-derived cells. *Arch Dermatol* 139: 510-516.
59. Mansilla E, Marin GH, Sturla F, Drago HE, Gil MA, et al. (2005) Human mesenchymal stem cells are tolerized by mice and improve skin and spinal cord injuries. *Transplant Proc* 37: 292-294.
60. Millán-Rivero JE, Martínez CM, Romecin PA, Aznar-Cervantes SD, Carpes-Ruiz M, et al. (2019) Silk fibroin scaffolds seeded with Wharton's jelly mesenchymal stem cells enhance re-epithelialization and reduce formation of scar tissue after cutaneous wound healing. *Stem Cell Res Ther* 10: 126.
61. Somal A, Bhat IA, Indu B, Singh AP, Panda BSK, et al. (2017) Impact of Cryopreservation on Caprine Fetal Adnexa Derived Stem Cells and Its Evaluation for Growth Kinetics, Phenotypic Characterization, and Wound Healing Potential in Xenogenic Rat Model. *J Cell Physiol* 232: 2186-2200.
62. Shohara R, Yamamoto A, Takikawa S, Iwase A, Hibi H, et al. (2012) Mesenchymal stromal cells of human umbilical cord Wharton's jelly accelerate wound healing by paracrine mechanisms. *Cytotherapy* 14: 1171-1181.
63. Ertl J, Pichlsberger M, Tuca AC, Wurzer P, Fuchs J, et al. (2018) Comparative study of regenerative effects of mesenchymal stem cells derived from placental amnion, chorion and umbilical cord on dermal wounds. *Placenta* 65: 37-46.
64. Zhao G, Liu F, Lan S, Li P, Wang L, et al. (2015) Large-scale expansion of Wharton's jelly-derived mesenchymal stem cells on gelatin microbeads, with retention of self-renewal and multipotency characteristics and the capacity for enhancing skin wound healing. *Stem Cell Res Ther* 6: 38.
65. Yoshikawa T, Mitsuno H, Nonaka I, Sen Y, Kawanishi K, et al. (2008) Wound therapy by marrow mesenchymal cell transplantation. *Plast Reconstr Surg* 121: 860-877.
66. Arno AI, Amini-Nik S, Blit PH, Al-Shehab M, Belo C, et al. (2014) Human Wharton's jelly mesenchymal stem cells promote skin wound healing through paracrine signaling. *Stem Cell Res Ther* 5: 28.
67. Zhang X, Reagan MR, Kaplan DL (2009) Electrospun silk biomaterial scaffolds for regenerative medicine. *Adv Drug Deliv Rev* 61: 988-1006.
68. Hashemi SS, Mohammadi AA, Kabiri H, Hashempoor MR, Mahmoodi M, et al. (2019) The healing effect of Wharton's jelly stem cells seeded on biological scaffold in chronic skin ulcers: A randomized clinical trial. *J Cosmet Dermatol* 18: 1961- 1967.
69. Peña-Villalobos I, Casanova-Maldonado I, Lois P, Prieto C, Pizarro C, et al. (2018) Hyperbaric Oxygen Increases Stem Cell Proliferation, Angiogenesis and Wound-Healing Ability of WJ-MSCs in Diabetic Mice. *Front Physiol* 9: 995.
70. Sun J, Zhang Y, Song X, Zhu J, Zhu Q (2019) The Healing Effects of Conditioned Medium Derived from Mesenchymal Stem Cells on Radiation-Induced Skin Wounds in Rats. *Cell Transplant* 28: 105-115.
71. Fong CY, Tam K, Cheyyatraivendran S, Gan SU, Gauthaman K, et al. (2014) Human Wharton's jelly stem cells and its conditioned medium enhance healing of excisional and diabetic wounds. *J Cell Biochem* 115: 290-302.
72. Yuana Y, Sturk A, Nieuwland R (2013) Extracellular vesicles in physiological and pathological conditions. *Blood Rev* 27: 31-39.
73. Bakhtyar N, Jeschke MG, Herer E, Sheikholeslam M, Amini-Nik S (2018) Exosomes from acellular Wharton's jelly of the human umbilical cord promotes skin wound healing. *Stem Cell Res Ther* 9: 193.
74. Zhao G, Liu F, Liu Z, Zuo K, Wang B, et al. (2020) MSC-derived exosomes attenuate cell death through suppressing AIF nucleus translocation and enhance cutaneous wound healing. *Stem Cell Res Ther* 11: 174.



Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752

Submit Your Manuscript: <https://www.heraldopenaccess.us/submit-manuscript>