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The effect of mesenchymal stem cells combined with platelet-rich plasma on skin wound healing

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Summary

Introduction: Mesenchymal stem cells (MSCs) are multipotent stem cells that have the potential of proliferation, high self-renewal, and the potential of multilineage differentiation. The differentiation potential of the MSCs in vivo and in vitro has caused these cells to be regarded as potentially appropriate tools for wound healing. After the burn, trauma or removal of the tumor of wide wounds is developed. Although standard treatment for skin wounds is primary healing or skin grafting, they are not always practical mainly because of limited autologous skin grafting.

Evidence Acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, PubMed (NLM), LISTA (EBSCO), and Web of Science have been searched.

Evidence Synthesis: For clinical use of the MSCs in wound healing, two key issues should be taken into account: First, engineering biocompatible scaffolds clinical use of which leads to the least amount of side effects without any immunologic response and secondly, use of stem cells secretions with the least amount of clinical complications despite their high capability of healing damage.

Conclusion: In light of the MSCs' high capability of proliferation and multilineage differentiation as well as their significant role in modulating immunity, these cells can be used in combination with tissue engineering techniques. Moreover, the MSCs' secretions can be used in cell therapy to heal many types of wounds. The combination of MSCs and PRP aids wound healing which could potentially be used to promote wound healing.

KEYWORDS
mesenchymal cell, stem cell, wound, wound healing

1 | INTRODUCTION

Regarding the function and suppressive property of mesenchymal stem cells (MSCs), this article seeks to investigate the use of the MSCs as a healing tool to treat wounds and their role in clinical use. Currently, different approaches are adopted to accelerate the process of healing of normal wounds, diabetic ulcers, and burns, including the use of antiseptics, antibiotics, cleaning wounds in different ways, appropriate bandaging, and the use of electrical stimulation, ultrasound, magnetic waves, lasers, nanoparticles, some cytokines and growth factors, and some chemical compounds.[1,2] These treatments are costly and difficult to apply. Therefore, a novel therapeutic approach is needed to heal chronic wounds. In the recent years, there has been a great interest in the use of stem cells to treat different diseases. The MSCs are a kind of stem cells that are currently being widely investigated. Stem cell-based therapies have been reported to be successfully used to heal and regenerate some tissues, and the MSCs have been demonstrated to have many therapeutic capabilities. These multipotent stem cells can differentiate into many types of the cells particularly mesenchymal cells such as fibroblasts, myoblasts, cardiac muscle, cartilage,

and bone as well as some nonmesenchymal cells such as neurons and hepatocytes. Besides that, they can produce certain growth factors and cytokines that accelerate healing process at sites of damage. Moreover, MSCs have been demonstrated to have the capability of healing wounds in animal models and diabetic mice.[3-5] Recent studies have shown that these cells can obtain the phenotype of germ line cells under appropriate induction conditions, which represents the MSCs potential to differentiate nonmesenchymal cells. In addition to being present in bone marrow, these cells are found in specialized tissues such as skeletal muscle, adipose tissue, synovial membrane, umbilical cord blood, and placenta.[6-9]

2 | PLATELET-RICH PLASMA

Platelet-rich plasma (PRP), also named autologous platelet gel, is principally an increased concentration of autologous platelets suspended in a small volume of plasma after centrifugation.[10] PRP was first defined in 2007 as a preparation of platelets present in a small volume of plasma containing a large number of growth factors.[11] PRP, which can be simply isolated from whole blood, is regularly used for wound healing. Recent findings proposed that platelet concentrates contained multiple functional growth factors, and cytokines might be used as cell therapy.[12] Platelets are rich in many growth factors, including PDGF, TGF-β1, VEGF, EGF, bFGF, and hepatocyte growth factor.[13] Studies have revealed that PRP may inhibit excessive early inflammation and interact with macrophages to improve wound healing.[14] Growth factors in platelets are generally in an inactive form, and they need to be activated. A platelet gel is produced by activating PRP with thrombin or CaCl2 to polymerize fibrinogen into a fibrin gel, which activates platelets to release growth factors into the wound.[15] Exogenous growth factors have been used experimentally to change wound healing. Effective delivery of the platelet-derived growth factors to a localized site of injury is significant. Fibrin sealant and fibrin glue are two methods for the sustained delivery of PRP-derived growth factors to injured tissue. Fibrin sealants are intended to mimic the final steps of the blood coagulation cascade, forming a stable, physiological fibrin clot that assists homeostasis and wound healing. Fibrin sealants, which have been accepted for hemostasis in the United States and Europe, are occasionally utilized to promote wounds healing.[16] Clinically, fibrin sealant has caused a low rate of infection and stimulated healing.[17] Fibrin glue provides a suitable carrier, which both delivers the growth factors to the wound and releases them at a steady rate.[18,19] The goal of this study was to evaluate the use of MSCs alone or in combination with PRP in the wound-healing process and an updated review of stem cell applications in burns and wound healing.

3 | EVIDENCE SYNTHESIS

3.1 | Action mechanisms of the MSCs in wound healing

Production and secretion of cytokines have been reported to be the main functions of the MSCs in wound healing. The MSCs exert pharmaceutical effects in healing wounds and lead to increase in collagen, its proliferation, and migration as well as its secretion in human dermal fibroblasts (HDFs) through activating them. Growth and induction factors released from the MSCs activate keratinocytes and dermal fibroblasts and contribute to wound healing through a paracrine mechanism. The MSCs can play a role in wound healing in two ways: first, differentiation into some other cells such as fibroblasts, epithelium, and keratinocytes [20-23] and secondly, the effects induced by paracrine that cause increase in angiogenesis, neovascularization, de-epithelization, synthesis of collagen, and ultimately wound healing through releasing various cytokines and growth factors Figure 1. When stem cells are used for burn, their paracrine effects cause a change in wound environment and the wound is healed. As well, the

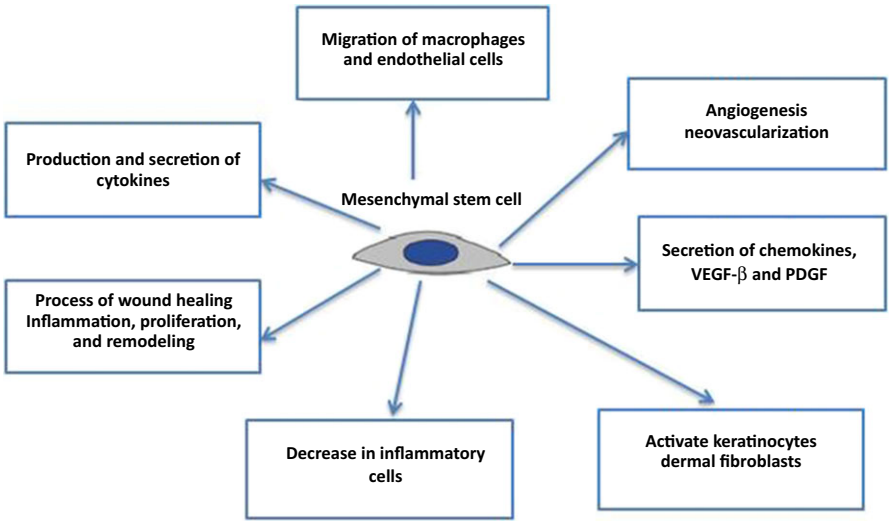

FIGURE 1 The mechanistic roles of MSCs in the wound healing. It has been proposed the mechanisms of acceleration of wound healing by MSCs are as follows: (1) activate keratinocytes and dermal fibroblasts, (2) increase angiogenesis, neovascularization, de-epithelization, (3) migration of macrophages and endothelial cells, (4) Secretion of chemokines particularly VEGF-β and PDGF,and (5) decrease in inflammatory cells

stem cells are effective in cell differentiation.[24-27] In vitro studies have demonstrated that umbilical cord MSCs can differentiate into keratinocytes and, therefore, have the potential to treat both autologous and homologous skin traumas.[28,29] In vitro, the culture of the MSCs contains large amounts of cytokines and growth factors that can cause migration of macrophages and endothelial cells and therefore acceleration of wound-healing process.[30] The MSCs have been reported to be able to activate fibroblasts via paracrine and cause acceleration of epithelialization. These cells were found to cause acceleration of filling up the scratch wound in culture dishes of fibroblasts and keratinocytes.[31] The MSCs can differentiate into keratinocytes and fibroblasts and therefore contribute to wound healing.[23,32] Stem cells cause mitigation of scarring, acceleration of wound closure, and increase in potential in wound healing.[33] Besides that, the MSCs can significantly accelerate wound healing when accompanied by polylactic acid-caprolactone scaffold.[34]

3.2 | Molecular assessment of wound healing

Angiogenesis refers to the formation of new capillaries from previous vessels which is necessary for wound healing. Angiogenesis is considered one of the most important events in wound healing. Ang-1, Ang-2, VEGFα are angiogenic stimuli and play a fundamental part in the process of wound healing. Histological examination and assessment of formation of endothelial cell network using hematoxylin-eosin and acridine orange staining, real-time PCR for Ang-1, Ang-2, VEGFα can be used to investigate wound healing after use of the MSCs.[35]

3.3 | Mechanisms of the MSCs in immune modulation

The MSCs play part in the process of wound healing in three phases: inflammation, proliferation, and remodeling. The direct effect in modulating the immune response caused by proinflammatory factors such as TNFα and IFNγ and increasing the concentrations of anti-inflammatory factors including interleukin 10 and interleukin 4 are important mechanisms of the MSCs which can be used to heal wounds particularly chronic ones.[36-38] Furthermore, studies have shown that the MSCs secrete the known mediators of wound healing including growth factors, cytokines, and chemokines particularly VEGF-β and PDGF [30,39,40] Moreover, they release mytogenes that increase proliferation of keratinocytes, skin fibroblasts, and endothelial cells.[40,41] Studies on diabetic mice have indicated that the MSCs cause increase in epithelialization and angiogenesis and therefore facilitate wound healing.[42] Moreover, the MSCs' transfer on the surface of burn-induced deep wounds causes a decrease in inflammatory cells, the formation of new vessels, and granulation of the tissue.[43]

3.4 | Mesenchymal stem cells combined with PRP for healing burn

Burn is one of the most common and destructive traumas, and its treatment brings stupendous costs for healthcare systems worldwide. It is highly necessary to conduct studies on the acceleration of wound-healing process and re-epithelization for certain reasons such as incomplete healing of burns, long-term treatments, stupendous treatment costs, and burn-induced secondary complications.[44] Conventional treatments for burn are washing the wound on a daily basis, removing dead tissues, antibiotic bandaging till the formation of granulation tissue, and transplantation. New generation treatments consist of cell therapy and use of growth factors such as platelet-derived ones.[45] Within the past decade, cell therapy has played a significant role in improving different diseases such as burns. MSCs can exert pharmaceutical effects in repairing skin. In light of the evidence on the differentiation of the MSCs into the precursors of bone, adipose, and germ line in vitro, their confirmed potential to produce specialized lines of different tissues as well as a large number of studies with these cells, they can also be used to treat burn wounds Table 3. Besides that, it can be recommended to use platelet cryogel alongside the MSCs given platelet-derived growth factors' effect on the MSCs differentiation and proliferation. This approach can relatively accelerate repair process and healing of burn-induced wounds. Platelet gel is a plasma which is rich in thrombin and calcium-activated platelets that causes tissue repair, cell migration, cell proliferation, angiogenesis, extracellular matrix synthesis, and acceleration of epidermal, epithelial, and endothelial regeneration in treating burn.[35,46,47] Platelet granules contain not only growth factors but also some other biological compounds such as serotonin, catecholamines, and antibacterial proteins.[48,49] The MSCs were used to treat burn in humans for the first time in 2005 in Russia. Five female patients were treated with allogeneic MSCs with promising outcomes.[20] A phase I and II clinical trials on allogeneic cell therapy in patients with acute burn were started in China in 2011 to investigate umbilical cord MSCs' efficacy in such patients. The use of activated platelets is more efficacious than other standard treatments for acute wounds particularly burns.[21] Transplantation of human umbilical cord (HUC)-MSCs can effectively help improve burn wounds in mice. These findings provide a theoretical basis to investigate the further clinical use of HUC-MSCs in burn sites.[22] In light of the above mentioned, the effects of the simultaneous use of platelet-derived growth factors and the MSCs in accelerating the process of burn-induced wound healing have been less frequently studied.

3.5 | Application of PRP and MSCs in skin wound healing

Platelets produce certain factors such as PDGF and TGF-β that play a role in proliferation, chemotaxis, and production of extracellular matrices and angiogenesis[41,42]; in addition, VEGF and PDGF play a fundamental role in hemostasis, cell proliferation, and wound healing.[13,50-52] Platelet-derived platelet cryogel (PRP) is widely used in wound healing.[13,51,53] Platelet cryogel is used as a wound-healing agent in facial surgery,[54] healing of acute trauma-induced and cutaneous wounds, bone repair and regeneration,[55] and healing of diabetic foot ulcers.[56] When activated, the platelets present in the PRP

secrete certain factors that cause an increase in the number of the MSCs and their survival. These factors induce the S phase of cell cycle and increase the number of the cells. Several studies have demonstrated the optimal effect of PRP on the growth of adipose tissue-derived MSCs[57,58] and bone marrow-derived MSCs Table 1.[59] Activation of PRB/Akt pathway is one of the molecular mechanisms potentially involved in the increased growth of the MSCs.[60] Inactivation of caspase-3 which is a key effective factor in apoptosis pathway is another potentially involved mechanism.[61] Umbilical cord-derived PRP has recently been reported to have greater potential to increase the growth of the MSCs. Another possible mechanism is that the PRP causes an increase in cellularity at transplantation site through increasing cell proliferation and utilizing the MSCs further. Analysis of the secretions released from the platelets demonstrated that the platelets released certain proteins that could contribute to the phases of wound healing independently or in combination.[56] Moreover, it has been demonstrated that mere use of some factors such as PDGF is not much successful in wound healing (Tables 2 and 3).[56,62]

4 | DISCUSSION

Wound healing is a complex physiological process, which contains numerous biological and molecular events such as cell migration and proliferation, extracellular matrix (ECM) deposition, angiogenesis, and remodeling.[63] New approaches to promote wound healing mainly depend on PRP, cell therapy, and 3-dimensional reconstruction to facilitate angiogenesis and epithelial propagation and decrease inflammation. Therefore, exploring new approaches to reduce the harm caused by wound healing in humans is of central importance.[64]

Many studies have been conducted on the MSCs whose therapeutic use is one of their most important and difficult utilizations. According to many studies that have been conducted on the MSCs, we can briefly argue that these cells are particularly important from therapeutic perspectives for certain reasons including being localized at the inflammation site in tissue wounds after being injected, having multilineage differentiation properties, and serving as multiple bioactive molecules that are able to induce healing in damaged cells. Thanks to certain differentiation properties, self-renewal, secretion of

TABLE 1 Effect of mesenchymal stem cells and platelet-rich plasma in wound healing

MSC source/Interventions	Study model	Main results	Ref
BM-MSCs, PRP	Rat burn	Histopathology of burn skin was improved in all treated groups particularly MSCs pretreated with PRP 20 d after burn.	35
ADSCs, fibrin gels	Rodent wounds mice	ADSCs are able to form tubular structures within fibrin gels and may also contribute to faster wound healing, as compared with no treatment or to wounds treated with fibrin gels devoid of ADSCs.	75
BMSCs cultured in a fibrin spray	Murine and Human	Autologous bone marrow-derived MSC can be safely and effectively delivered to wounds using a fibrin spray system.	76
Fibrin glue combined with BMSCs	Scalded skin of rat	Allogeneic BMSCs mixed with fibrin glue can contribute to the quick formation of a film-like gel over the scald wounds, which might be of significance for emergency treatment and skin-grafting operations.	77
ADSCs, PRP	Fibroblast, keratinocyte (in vitro)	Results propose an association between ADSC and PRP soluble mediators, which could potentially be used to promote healing and re-epithelialization in cutaneous ulcers.	69
Fetal mesenchymal Stem, PRP	Patients suffering from skin ulceration	PRP may act as a regulator of cell migration and wound healing.	72
MSCs isolated from amniotic fluid, PRP	Neonatal foal (Severe decubitus ulcers in a septic neonatal foal)	Healing was faster using MSCs + PRP, and at 7 mo, an ulcer treated with aloe gel was still not completely healed .	78
BM-MSCs, PRP on a collagen matrix	Lewis rat	This study shows that the addition of BM-MSCs to platelet-rich plasma leads to a marked improvement, muscle survival along the scar edges with improved collagen abundance and vascularization.	79
BM-MSCs, PRP	Diabetic rat	The combination of BMSCs and PRP aids diabetic wound healing.	71
MSCs, PRP	Diabetic mice	Animals treated with MSCs alone showed a similar level of re-epithelialization of cutaneous lesions to those treated with MSC plus PRP, and no significant difference was found between the two treatments.	80
PB-MSCs, PRP	Sheep (experimentally injured deep digital flexor tendons)	Results indicate that the combined use of PRP and MSCs did not produce an additive or synergistic regenerative response and highlighted the predominant effect of MSCs on tendon healing, enhanced tissue remodeling, and improved structural organization.	81

ADSCs, adipose tissue-derived stem cells; BM-MSCs, bone marrow mesenchymal stem cells; MSCs, mesenchymal stem cells; PB-MSCs, peripheral blood-derived MSCs; PRP, platelet-rich plasma.

TABLE 2 Growth factors present in platelet-rich plasma and their functions[62]

Growth factor	Source	Functions
TGF	Platelets, bone extracellular matrix, macrophages, monocytes, and neutrophils	Stimulating undifferentiated mesenchymal stem cells, regulating proliferation of endothelial cells, fibroblasts, and osteoclasts, regulating synthesis of collagen, stimulating chemical absorption and angiogenic properties, inhibiting the proliferation of macrophages and lymphocytes.
bFGF	Platelets, macrophages, mesenchymal cells	Stimulating growth and differentiation of cartilage and bone cells, proliferating mesenchymal cells.
PDGF	Platelets, osteoclasts, endothelial cells, and macrophages	Proliferating mesenchymal and bone cells, chemical adsorption, and proliferating fibroblasts.
EGF	Platelets, macrophages, and monocytes	Stimulating chemical adsorption of vascular cells, regulating release of collagen, stimulating the proliferation of mesenchymal and epithelial cells.
VEGF	Platelets and endothelial cells	Increasing vascular permeability, stimulating the proliferation of endothelial cells.

TABLE 3 Studies of mesenchymal stem cell-based therapies for wound healing and burn

MSC source/ Interventions	Study model	Main results	Ref
ADSCs, activin B	C57BL/6 mice	Results showed that activin B was able to activate JNK and ERK signaling pathways to induce actin stress fiber formation and ADSC migration to promote wound healing.	82
ADSCs	Rabbit	Transplantation of ADSCs can promote the wound healing of skin-deep partial-thickness scald wound of rabbit and shorten the wound-healing time.	83
hUCMSCs	Balb/c mice	Wound dressing model of hUCMSCs-alginate gel mix can promote wound healing through paracrine signaling.	84
BM-MSCs, seeded in a collagen-chitosan sponge scaffold	Diabetic rats	BM-MSCs exhibited a significant upregulated expression of proangiogenesis factors, including HIF-1alpha, VEGF, and PDGF, following hypoxia pretreatment. In vivo, hypoxia pretreatment of the skin substitute observably accelerated wound closure via the reduction in inflammation and enhanced angiogenesis in diabetic rats.	85
3-D graphene foams loaded with BM-MSCs	Rat	Graphene foams scaffold could guide the wound-healing process with reduced scarring, and the MSCs were crucial to enhance vascularization and provided a better quality neoskin.	86
Epigallocatechin-3-gallate, along with MSCs	Rat	EGCG, together with MSCs, can promote skin wound healing likely through their combinational effects in modulating chronic inflammation.	87
MSCs, Chitosan gel	Albino rat	MSCs enhanced the healing process of wound closure more than chitosan gel treatment. Furthermore, MSCs, injected intradermally, were more efficient in accelerating wound healing than any other mode of treatment.	88
Placenta-derived MSCs	Mice	MSCs promote wound healing through release of proangiogenic factors as VEGF, increase healing promoting factors as integrin beta1 and beta3, and decrease proinflammatory cytokines as ICAM-1.	89
WJ-MSCs	Mice	Under experimental conditions, WJ-MSCs enhanced skin wound healing in an in vivo mouse model.	90
AF-MSC	ICR mice	AF-MSC enhances wound healing through the increase in hypoxia-induced paracrine factors via activation of TGF-beta/SMAD2 and PI3K/AKT pathways.	91
BM-MSCs	Diabetic foot rat	Healing process in diabetic rats was ameliorated by transplantation of BM-MSCs, and this amelioration might be accounted for by the modification of keratinocyte functions.	92
WJ-MSCs on gelatin microbeads	Balb/C mice	hWJ-MSC can be expanded markedly in gelatin microbeads, while retaining MSC surface marker expression, multipotent differential potential, and expression of core transcription factors. These cells also efficiently enhanced skin wound healing in vivo, in a manner comparable to that of hWJ-MSC obtained from 2D culture.	93

(Continues)

TABLE 3 (Continued)

MSC source/ Interventions	Study model	Main results	Ref
BMSCs	BALB/c mice	CXCR4-overexpressing BMSCs migrate in an enhanced manner to skin wounds in a SDF-1-expression-dependent manner, thereby reducing the skin wound-healing time.	94
MSC	C57BL/6 mice	MSC-released TSG-6 was identified to improve wound healing by limiting Mphi activation, inflammation, and fibrosis. TSG-6 and MSC-based therapies may thus qualify as promising strategies to enhance tissue repair and to prevent excessive tissue fibrosis.	95
BM-MSCs	Burn in rat	This study demonstrates the therapeutic effectiveness of intradermal application of MSCs in a rat model of deep burns, providing basis for future regenerative therapies in patients suffering from deep burn injuries.	96
MSC-seeded SIS	Burn in rat	Small intestinal submucosa (SIS) alone and MSC-seeded SIS were able to accelerate the burn wound closure by enhancing granulation tissue formation, increasing wound maturity, improving revascularization, and inducing the proliferation of neoepidermal cells.	97
hUCMSCs	Burns in rats	hUCMSCs transplantation could suppress secondary inflammatory reaction by lowering inflammatory cytokines after burning, thus, promoting wound healing and scald repair.	98
BM-MSCs	Mice model burn	Results suggest that BM-MSC transplantation can effectively improve wound healing in a mouse model of burn injuries.	99
hUCMSCs and their exosomes	Rat skin burn model	Results suggest that hUCMSCs -Ex-mediated Wnt4 induces β-catenin activation in endothelial cells and exerts proangiogenic effects, which could be an important mechanism for cutaneous wound healing.	100
Allogeneic MSC and autologous culture Modified monocytes	Porcine burn model	A single application of allogeneic MSC improves the rate of burn wound healing and improves the histological appearance of the burn wound.	101

3D, three-dimensional; ADSCs, adipose tissue-derived stem cells; AF-MSCs, amniotic fluid mesenchymal stem cells; BM-MSCs, bone marrow mesenchymal stem cells; hUCMSCs, human umbilical cord mesenchymal stem cells; ICR mice, imprinting control region (ICR) mice; MSCs, mesenchymal stem cells; TSG-6, TNF-stimulated gene 6; WJ-MSCs, Wharton's Jelly-mesenchymal stem cells.

a wide spectrum of cytokines, a unique ability to bind to the damaged cells, and migration to the sites of injury, the MSCs are considered appropriate alternatives for cell therapy and gene therapy. Besides that, these cells have been found to be suitable tools for some therapies such as cell-based tissue engineering and wound healing because of having immunity-modulating property. Recent studies have enhanced out understanding of the MSCs to some extent and provided the evidence that these cells can be used as a promising tool to treat different diseases especially wounds. In vitro findings on different animal models and the clinical trials' results have demonstrated that the MSCs are suitable tools for wound healing.

Although the MSCs have been successfully utilized to treat diabetic ulcers, many studies have reported successful transplantation of these cells in different cases, and even they have been used to modulate immune system, these cells appear to have immunogenic property and, in practice, the recipient's immunosuppression should be used to stabilize the transplantation of the MSCs.[65] Moreover, a number of studies have demonstrated that the mesenchymal cells' effect on wound-healing process is mainly due to their secretion of paracrine. It is, therefore, possible to not only use their advantages but also resolve the potential problems related to the cells' presence in the body through removing the cells and using their secretions in new therapeutic approaches.[65,66] To heal diabetic ulcers in mice, an optimal culture medium named conditioned medium, derived from bone marrow MSCs, is used. In fact, this medium contains metabolites, cytokines, growth factors, and extracellular matrix proteins that are released into the medium by the mesenchymal cells. The effect of this optimal culture medium in repairing certain tissues, especially skin wounds, and the bone fracture has been reported.[22,30,67] Therefore, use of the factors secreted by autologous or homologous cells seems the best approach to utilize the capabilities of the MSCs, without being faced with their potential immunogenicity or tumorigenicity problems, to heal skin wounds and diabetic ulcers. In a study, this medium was prepared from the MSCs and used to heal wounds in mice. This medium was found to be significantly effective in healing wounds.[68]

4.1 | MSCs in combination with PRP for the treatment of wound healing

Combined treatment of MSCs and PRP may increase fibroblasts and keratinocytes in wound skin. Fibroblasts healing, remodel wounded skin, and the migration of keratinocytes promote re-epithelialization through the healing process.[69] MSCs and PRP improve the

degeneration of articular cartilage in the surgically induced osteoarthritis animal model. MSCs and PRP treatment encourage the downregulated expression of TNF-α compared to the diseased group, and the combined treatment may be beneficial as an inflammatory regulator.[70] The combined effect of MSCs and PRP has been evaluated by Lian et al[71] who found that the wound-healing rates were significantly higher in the MSCs plus PRP group than in the other groups. The synergistic effect of MSCs and PRP for the healing of refractory wound healing in a diabetic rat model was also evaluated. MSCs plus PRP group showed 1.5-fold and 1.4-fold higher TGF-β1 expression than PRP and MSCs alone, respectively. This increased expression might promote the synthesis of collagen proteins and integrin in fibroblasts and increased epithelial cell migration. MSCs and PRP could induce a stronger angiogenic response in healing wounds. Besides, wounds treated with MSCs plus PRP revealed 12.5 blood vessels compared to 8 and 4.5 blood vessels in wounds treated with MSCs alone and PBS.[71] PRP concentrations stimulated proliferation and migration of adipose-derived stem cells (ADSC) and fibroblasts in vitro. Furthermore, keratinocyte proliferation could be stimulated by ADSC paracrine action. These results suggested an association between ADSC and PRP soluble mediators, which could potentially be used to promote healing and re-epithelialization in wound healing.[69]The presence of PRP in the amniotic fluid mesenchymal stem cells (AF-MSCs) medium substituting FBS resulted in an important stimulation of the migration ability and the proliferation rate of AF-MSCs.[72] The highly expressed factors such as PDGF and MMP9 in PRP appeared to act positively in inducing migration of these cells. Reduction in SDF-1 a, which was observed when MSCs were cultured with PRP, led to a decrease in migratory capacity and theoretically an increase in MSC concentration within the wound bed.[73,74] PRP and MSCs independently led to increasing neovascularization in wounded tissues.[29]

5 | CONCLUSION

MSCs have been demonstrated to improve wound healing through increased angiogenesis, re-epithelialization, and granulation tissue formation. MSCs have an active role in the process of wound healing, acting via paracrine interactions, accelerating wound closure, promoting resolution of wound inflammation, regulating extracellular matrix remodeling, encouraging regeneration of skin with normal construction and function, and suggesting great therapeutic potential. MSCs express keratinocyte-specific markers and high levels of VEGF and Ang-1 suggest that MSCs promote wound healing by differentiation and release of proangiogenic factors. PRP is employed to wound healing, because of several growth factors crucial for healing, such as PDGF, TGF, IGF, and EGF, which are concentrated in platelets. These factors not only regulate cell migration and proliferation but also remodel the extracellular matrix (ECM) and promote angiogenesis, and create a useful environment that enhances wound healing. PRP is a rich source of growth factors that stimulate angiogenesis in wounds. PRP stimulates MSCs proliferation, preserves MSCs multipotency, and does not interfere with any lineage differentiation in a controlled nontumorigenic manner, a property that is of high value not only for cell manufacturing but also for the clinical applications. PRP may serve as a regulator of cell migration and wound healing and promote MSCs migration and wound-healing process. PRP may offer a suitable microenvironment for MSCs to promote proliferation and differentiation. PRP can be a powerful tool to attract cell populations, such as MSCs in the wound area. PRP can be an alternate substitute for bovine serum for growing MSCs. The use of MSCs, PRP, and MSCs together with PRP improves and accelerates wound healing. PRP together with MSCs may represent a promising approach for the treatment of wound healing.

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