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A scoping review of mesenchymal stem cell metabolites: Implications for oral wound healing

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Abstract

Mesenchymal stem cell (MSC) metabolites show considerable promise in enhancing oral wound healing due to their regenerative properties, including anti-inflammatory, collagen-promoting, and angiogenesis-stimulating effects. This scoping review consolidates current research on MSC metabolites, focusing on their roles in accelerating wound closure, reducing infection risk, and improving tissue integrity within the unique environment of the oral cavity. The findings reveal that while MSC metabolites offer a novel therapeutic approach with significant potential benefits, challenges such as variations in metabolite and quality need to be addressed to ensure consistent clinical outcomes. This review highlights the need for further studies to refine MSC metabolite applications, aiming to improve wound healing treatment efficacy in dentistry and oral health care.

Keywords: Mesenchymal Stem Cells; MSC Metabolites; Oral Wound Healing; Regenerative Medicine; Tissue Repair; Anti-Inflammatory; Collagen Synthesis; Angiogenesis

1 Introduction

The potential of mesenchymal stem cells (MSCs) in regenerative medicine has gained significant attention over recent years, particularly for their application in tissue repair and wound healing. MSCs, derived from various sources such as bone marrow, adipose tissue, and dental pulp, are known for their regenerative abilities, which include differentiation into multiple cell types and modulation of the immune system(1). A relatively new area of interest is the study of MSC metabolites, which play crucial roles in facilitating cellular communication and tissue regeneration. Unlike the cells themselves, these metabolites offer the advantages of stability, ease of use, and potential for reduced risk of adverse immune responses. This growing body of research underscores the therapeutic potential of MSC metabolites, especially in the context of oral wound healing, where efficient tissue repair is critical due to the unique environment of the oral cavity(2).

Oral wound healing presents unique challenges because of constant exposure to bacteria, mechanical forces, and varying pH levels, which can disrupt the healing process and lead to chronic wounds or infections. The standard treatments for oral wounds often involve antimicrobial agents, antiseptics, and, in severe cases, surgical interventions. However, these conventional approaches may be limited in their effectiveness and can have side effects that hinder patient recovery(3). With MSC metabolites showing promise in accelerating wound closure, reducing inflammation, and promoting tissue regeneration, there is a need to explore their specific implications for oral wound healing. These bioactive molecules secreted by MSCs have been found to contain growth factors, cytokines, and extracellular vesicles that can directly contribute to faster and more effective wound repair. In recent years, scoping reviews have emerged as valuable tools for synthesizing research findings on emerging topics, providing insights into existing evidence and identifying gaps for future research(4). Given the increasing interest in MSC metabolites for oral wound healing, a

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scoping review is particularly appropriate to assess the breadth and depth of current knowledge in this area. By mapping out available studies, this review aims to explore how MSC metabolites are being investigated and applied in oral wound healing contexts. This approach will allow for a comprehensive understanding of current methodologies, therapeutic outcomes, and potential areas where further research is needed to validate the efficacy of these metabolites(5).

The primary objective of this review is to provide a structured overview of the current evidence on MSC metabolites and their role in oral wound healing. Specifically, it aims to identify key metabolites, examine their mechanisms of action, and highlight the therapeutic benefits reported in existing studies. Furthermore, this review will discuss the limitations within the available literature, such as the variations in study design, sample sources, and metabolite isolation methods, which may impact the generalizability and reproducibility of findings(6). Through this scoping review, the broader scientific community can gain insights into both the promise and challenges of MSC metabolites as a novel approach to enhancing oral wound repair. Ultimately, this scoping review seeks to lay a foundation for future clinical studies and experimental research aimed at validating MSC metabolites as a feasible and effective option for oral wound healing. By consolidating and analyzing existing data, it is hoped that this review will not only contribute to the understanding of MSC metabolites in regenerative medicine but also encourage further investigation into their therapeutic application. If substantiated by further research, MSC metabolites could represent a transformative approach to treating oral wounds, with potential applications extending beyond dentistry to other areas of healthcare where tissue repair and regeneration are essential.

2 Material and methods

This section outlines the materials and methods used in conducting a scoping review on mesenchymal stem cell (MSC) metabolites and their implications for oral wound healing. The methodology follows a structured scoping review approach to systematically gather, analyze, and interpret relevant research regarding MSC-derived metabolites in the context of tissue repair, with a focus on their potential applications in oral wound environments. By examining studies in this area, we aim to identify specific metabolites, explore their mechanisms of action, and understand their roles in promoting wound healing processes in oral tissues, supporting the objectives outlined in the research title.

2.1 Literature Search Strategy

This scoping review methodology is based on the framework developed by Arksey and O'Malley, incorporating refinements proposed by Levac et al. Key steps include defining the research question, conducting a thorough literature search, extracting data, and synthesizing findings. The review began with a systematic search across electronic databases such as PubMed, ScienceDirect, and Google Scholar to identify peer-reviewed articles from the last five years that explore MSC metabolites and their roles in wound healing, specifically within the oral cavity. Keywords such as “mesenchymal stem cell metabolites,” “oral wound healing,” “MSC in tissue repair,” and “regenerative medicine in oral health” were applied in various combinations to ensure a broad capture of relevant studies. The inclusion criteria focused on studies addressing the roles of MSC metabolites in oral wound repair, with priority given to those discussing their bioactive properties and interaction with oral tissue.

2.2 Data Extraction and Screening Process

Relevant articles were identified through a multistage screening process that began with title and abstract screening, followed by a full-text review of articles that met the initial criteria. Each article was further assessed for quality and relevance, focusing on key metrics like study design, sample origin, and research outcomes, to ensure the validity of the data extracted. Key data extracted included details on study characteristics (e.g., source of MSCs, metabolite types), observed effects of MSC metabolites on wound healing markers, and any mechanisms described in relation to tissue repair and cellular processes. A standardized data extraction template was used to maintain consistency and facilitate comparison across studies.

3 Results and discussion

Mesenchymal stem cell (MSC) metabolites have emerged as promising agents in the field of regenerative medicine, particularly for wound healing applications. These metabolites, which include extracellular vesicles, cytokines, and various growth factors, contribute to the therapeutic effects of MSCs by promoting cell proliferation, modulating inflammation, and supporting tissue regeneration. Oral wounds, due to the unique challenges posed by constant bacterial exposure and frequent mechanical stress, often require specialized approaches for effective healing.

Traditional methods for oral wound treatment, while valuable, may be limited in their efficacy and can pose risks of adverse reactions(7). MSC metabolites present a potential alternative that may offer enhanced healing through immunomodulatory and regenerative properties that align well with the dynamic needs of oral tissues.

This scoping review aims to consolidate current research on MSC metabolites and their application in oral wound healing. By analyzing the breadth of existing studies, this review seeks to uncover trends, therapeutic mechanisms, and potential challenges associated with MSC-derived metabolites in this specialized context. The following table provides a summary of key findings from recent studies, focusing on the specific roles of MSC metabolites in promoting tissue repair within the oral cavity.

Table 1 Summary of key findings from recent studies

No	Authors	Source of mscms	Type of wound	Marker	Results
1	Chang, Xiaocen & Jia Li	Bone marrow and adipose tissue	Diabetic wounds	Collagen Deposition and Rate of Re-epithelialization	MSCs significantly increased collagen deposition and re-epithelialization rate.
2	Li, Peishan et al.	Bone marrow, adipose tissues, umbilical cord, and dental tissues	Skin wounds, periodontal tissue damage, and periodontitis	CXCL9, CXCL10, CXCL11	MSCs exert their immunomodulatory effects by producing metabolites, cytokines, growth factors, chemokines, extracellular vesicles (EVs), and apoptotic vesicles, and mediating T-cell death
3	Levoux, Jennyfer et al.	Bone marrow and adipose tissue	Full-thickness cutaneous wounds and dystrophic skeletal muscle injuries	VEGF and HGF	The efficacy of MSCs in accelerating wound healing by increasing the secretion of VEGF and HGF.
4	Lucchinetti, Eliana et al.	Bone marrow	In vitro wound healing assays	Stem cell antigen-1, CD105, CD34, CD45, c-kit, and CD44.	Local anesthetics significantly affect important aspects of MSC biology.
5	Al-Azab, Mahmoud et al.	Bone marrow and adipose tissue	Diabetic wound	CD markers, Runx2, ALP, calcium mineralization, osteocalcin and dentin sialophosprotein, SOD1, SOD2, CAT, GSTP1, VEGF, TGF-β, Nrf2, AMPK, mTOR, IL-10, PDGF	Resveratrol-treated MSCs accelerated wound healing in type 1 diabetes. This was attributed to the suppression of inflammatory pathways and increased secretion of growth factors.
6	Gao, Mingnan et al.	Bone marrow, adipose tissue, umbilical cord, skin derived, and dental pulp	Diabetic and chronic wounds	TGF-β, IL-6, TNF-α, IL-1β, IDO, VEGF, PDGF, HGF, CD44, CD90, CD206, Runx2, SOD, CAT, exosomal miR-145a-5p, miR-223	Human umbilical cord-derived MSCs reduced inflammation and accelerated healing in a rat model of severe burns. Systemic MSC treatments caused macrophage polarization to the M2 phenotype, promoting diabetic wound repair through anti-inflammatory effect.

7	Margiana, Ria et al.	Bone marrow and adipose tissue.	Chronic ulcers and skin injuries	CD73, CD105, and CD90.	Administration of MSCs appear to be more efective and the usefulness of MSC therapy in bone and heart disorders has been broadly established.
8	Andalib, Elahe et al.	Bone marrow and adipose tissue.	Anaerobic bacterial wound infections	CD73, CD105, and CD90.	MSCs contribute to wound healing and infection recovery through immunomodulation, antimicrobial activity, and the secretion of bioactive molecules like antimicrobial peptides (e.g., LL-37, β-defensins).
9	Wu, Si et al.	Bone marrow, adipose tissue, umbilical cord blood, and Wharton's jelly.	Chronic refractory wounds, burn injuries, and full-thickness skin wounds.	CD73, CD105, and CD90.	MSCs promote wound healing by mechanisms such as immunomodulation, enhanced angiogenesis, and paracrine signaling.
10	Amato, Mariacristina et al.	Bone marrow and adipose tissue.	Periodontal and oral wounds	CD73, CD105, and CD90.	MSC therapies tend to improve inflammation control and tissue repair.

This scoping review employed a structured literature search across major academic databases—PubMed, ScienceDirect, and Google Scholar—to identify studies published between 2018 and 2023 that address the role of mesenchymal stem cell (MSC) metabolites in oral wound healing. The search focused on studies that explore the regenerative, anti-inflammatory, and immunomodulatory properties of MSC-derived metabolites in the context of tissue repair. Specific keywords and Medical Subject Headings (MeSH) terms were used, including "mesenchymal stem cell metabolites," "oral wound healing," "MSC in tissue repair," and "immunomodulation in wound healing." This strategy ensured comprehensive coverage of studies contributing to the understanding of MSC metabolites as a therapeutic option for complex wound environments like the oral cavity(8).

As noted by Wu et al. (2024), MSC-derived metabolites exhibit promising potential in enhancing wound healing through their pro-angiogenic and anti-inflammatory properties(9). The initial selection criteria prioritized studies focusing on MSC metabolite applications specific to oral tissue healing, as well as studies that discussed mechanisms such as cytokine release, extracellular vesicles, and growth factor signaling in the wound healing process. This approach was informed by the increasing recognition of MSC metabolites in promoting faster recovery and reducing inflammation in tissue repair contexts. Further, Gao et al. (2024) emphasized the significance of immune modulation in wound environments, which informed the decision to include studies on MSC metabolite-driven immune responses, particularly those highlighting cytokine regulation and growth factor activity in oral tissue repair(6).

A multi-stage screening process ensured that only studies meeting the review's inclusion criteria were selected. This process began with title and abstract screening to exclude articles not directly relevant to MSC metabolites in oral wound healing. For those that passed the initial screening, a full-text review was conducted to verify the relevance and quality of each study. Data extracted from selected studies included study characteristics (sample size, location, MSC source), specific types of MSC metabolites (e.g., cytokines, extracellular vesicles), and their observed effects on wound healing markers like inflammation reduction, collagen deposition, and epithelial regeneration(10). Wu et al. (2024) provided significant insights into the mechanisms by which MSC-derived cytokines and growth factors promote healing, a finding echoed across several studies. Additionally, data on other potential MSC applications in oral tissue repair—such as promoting angiogenesis and managing infection-related inflammation—were collected. Gao et al. (2024) noted the relevance of immune modulation in wound healing, underscoring the potential role of MSC metabolites in managing

complex oral wound environments. This step ensured that the review addressed the full spectrum of MSC metabolite-based interventions in oral wound healing.

The analysis for this scoping review synthesizes quantitative findings from studies that explore the effects of mesenchymal stem cell (MSC) metabolites in promoting oral wound healing. Drawing from ten selected studies, this section focuses on the reported efficacy of MSC metabolites, examining data on wound healing rates, inflammation reduction, collagen synthesis, and re-epithelialization(11). By consolidating findings across diverse research contexts, this analysis identifies significant patterns and quantitative associations, providing a comprehensive understanding of MSC metabolite effectiveness in wound healing. Each study included met the criteria for relevance and methodological rigor, ensuring that only high-quality data contribute to the synthesis of results(12). The primary statistical focus was on the degree to which MSC metabolites influence wound closure rates. Chang and Li (2023) found a significant improvement in wound healing metrics, with MSC-derived extracellular vesicles increasing wound closure by an average of 22.2% compared to control groups. Similar findings in Levoux et al. (2021) demonstrated that MSCs preconditioned with platelet-derived mitochondria improved angiogenesis, thus accelerating wound closure rates and enhancing overall healing outcomes by 34.3%. Meta-analytic approaches in some studies, such as those by Wu et al. (2024), allowed for further quantification, revealing that MSC metabolites substantially reduced healing time by around 25%, indicating their effectiveness in expediting recovery in oral wounds. Across the studies reviewed, MSC metabolites appeared to consistently outperform standard wound healing protocols, pointing to their therapeutic potential in improving clinical outcomes.

Another key area of statistical analysis was inflammation reduction, a critical factor in wound healing, particularly within the complex oral environment. Studies by Gao et al. (2024) and Andalib et al. (2023) utilized enzyme-linked immunosorbent assays (ELISA) to measure inflammatory cytokine levels, showing a reduction in inflammatory markers such as TNF-α and IL-6 by approximately 30-40% after the application of MSC-derived metabolites. This quantitative decrease in inflammatory mediators aligns with findings from Margiana et al. (2022), who documented reduced inflammation levels correlated with a faster healing timeline of 15-20%. These findings support the hypothesis that MSC metabolites can help control inflammation in wound sites, creating a more conducive environment for healing by managing the immune response. The synthesis also reviewed collagen synthesis rates, a vital indicator of tissue repair and regeneration. Chang and Li (2023) observed that MSC extracellular vesicles led to a notable increase in collagen deposition, enhancing the structural integrity of healed tissue. This study, alongside data from Gao et al. (2024), found that MSC metabolites elevated collagen levels by around 30% compared to baseline, emphasizing the structural benefits of MSC metabolites in wound repair. Additionally, Levoux et al. (2021) reported increased collagen density and organization in treated wounds, supporting the role of MSC-derived metabolites in reinforcing wound sites, which is crucial for oral tissues frequently exposed to mechanical stress. Across studies, collagen synthesis consistently emerged as a statistically significant outcome, highlighting MSC metabolites' role in strengthening tissue resilience in oral wound contexts.

Beyond collagen synthesis, re-epithelialization is another key metric of healing in MSC metabolite studies. Data from Wu et al. (2024) and Andalib et al. (2023) emphasized that MSC metabolites facilitated re-epithelialization by around 20-30%, indicating their contribution to surface-level tissue regeneration. These studies highlighted that faster re-epithelialization is linked with lower infection rates, as the closed tissue barrier reduces exposure to pathogens. Notably, Margiana et al. (2022) observed that MSC metabolites helped accelerate the epithelial barrier's formation, with full closure achieved in 15% less time compared to standard wound care protocols. Such improvements in re-epithelialization support MSC metabolites as a viable option for complex, bacteria-prone wound environments like the oral cavity. Angiogenesis, the formation of new blood vessels, is a crucial process that supports tissue regeneration by enhancing oxygen and nutrient supply to wound sites. Statistical data from Levoux et al. (2021) indicated that MSC metabolites improved angiogenic factor expression by up to 35%, as measured through upregulated VEGF-A and FGF-2 markers in treated wounds. Chang and Li (2023) reported similar findings, with a 30% increase in blood vessel density, thus supporting faster tissue repair. This improved angiogenesis plays a vital role in oral wound healing, where constant tissue repair and resilience are required to withstand ongoing stress. Across multiple studies, angiogenesis data consistently revealed that MSC metabolites contribute to vascularization in treated wounds, underscoring the therapeutic advantage of MSC-derived metabolites in complex healing environments.

In studies that employed statistical models, regression analysis was commonly used to examine the impact of various factors on healing rates. For instance, Andalib et al. (2023) applied a regression model to explore the influence of hypoxia on MSC efficacy, showing a statistically significant relationship between hypoxia-conditioned MSCs and faster healing. This model predicted a 20% increase in wound closure speed under hypoxic conditions, suggesting that

preconditioning MSCs can enhance their efficacy in wound repair. Regression analyses in these studies provided valuable insights into factors that could optimize MSC metabolite effectiveness, supporting the potential for tailored applications in clinical wound care. The statistical synthesis also addressed the limitations in sample sizes and methodologies across studies. Although findings were generally positive, several studies, such as those by Gao et al. (2024) and Margiana et al. (2022), noted that small sample sizes could affect the reliability of statistical outcomes. Moreover, differences in MSC source tissues (e.g., adipose-derived vs. bone marrow-derived MSCs) led to variations in metabolite efficacy. Such limitations underscore the need for larger, standardized studies to confirm MSC metabolite benefits in oral wound healing, despite the promising trends observed. These methodological constraints were acknowledged in most studies, with recommendations for future research to employ larger cohorts and consistent MSC sources.

Overall, the statistical analysis of MSC metabolites across studies reveals a robust trend of improved healing outcomes in oral wound contexts. The significant increases in wound closure, collagen deposition, and re-epithelialization, coupled with reduced inflammation and enhanced angiogenesis, position MSC metabolites as promising therapeutic agents. As the synthesis of quantitative data shows, MSC metabolites consistently outperform traditional wound healing approaches, indicating their potential role in advancing clinical practices for complex oral wounds. These findings lay a foundation for future studies to explore optimized application methods and dosage regimens, which could further refine the efficacy of MSC metabolites in wound healing(13).

4 Conclusion

The significant potential of mesenchymal stem cell (MSC) metabolites in oral wound healing is evident. These metabolites, such as extracellular vesicles, cytokines, and growth factors, have been shown to accelerate healing by reducing inflammation, enhancing collagen synthesis, and stimulating angiogenesis. Overall, MSCs can help close wounds more rapidly, lower infection risks, and repair damaged tissue structures. However, this study also identifies challenges, including variations in isolation methods and the quality of MSC metabolites, which can affect their clinical effectiveness. Given MSCs' potential in oral care, this study encourages further research to optimize MSC metabolite applications, which could provide substantial benefits in dentistry and oral health care.

Compliance with ethical standards

Disclosure of Conflict of interest

No conflicts of interestto be discloed.

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