Menstrual Blood-Derived Stem Cells: Mechanisms, Therapeutic Applications, and Future Perspectives

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Abstract : Menstrual blood-derived stem cells (MenSCs) have emerged as a unique, non-invasive, and ethically favorable source of mesenchymal stem cells with significant promise for regenerative medicine. MenSCs exhibit high proliferative capacity, multipotency, and immunomodulatory properties, and can be collected easily and periodically, distinguishing them from other adult stem cell sources. Mechanistically, MenSCs contribute to tissue repair through differentiation into target cell types, paracrine secretion of bioactive factors, immunomodulation, and homing to sites of injury. These properties have enabled MenSCs to demonstrate therapeutic potential in a wide range of preclinical and early clinical studies, including applications for gynecological disorders (such as intrauterine adhesions, endometriosis, and premature ovarian insufficiency), cardiovascular and liver diseases, neurodegenerative conditions, diabetes, and wound healing. Recent research has also highlighted the promise of MenSC-derived extracellular vesicles and exosomes as cell-free therapies, as well as the use of gene editing and engineered delivery platforms to enhance therapeutic outcomes. Despite these advances, challenges remain regarding the standardization of MenSC isolation and characterization, donor variability, and the need for long-term safety and efficacy data from large-scale clinical trials. Future research should focus on optimizing protocols, elucidating precise mechanisms of action, and addressing regulatory and safety concerns to fully realize the clinical potential of MenSC-based therapies in regenerative medicine.

I. INTRODUCTION

Menstrual blood-derived stem cells (MenSCs) have emerged as a promising, non-invasive, and ethically uncontroversial source of mesenchymal stem cells (MSCs) with significant potential in regenerative medicine and disease therapy. Since their discovery in 2007, MenSCs have been recognized for their high proliferative capacity, multipotency, immunomodulatory properties, and ease of collection, distinguishing them from other adult stem cell sources such as bone marrow and adipose tissue. Mechanistically, MenSCs exert therapeutic effects through differentiation into target cells, immunomodulation, paracrine signaling, and homing to injured tissues. Preclinical and clinical studies have demonstrated their efficacy in treating a wide range of conditions, including gynecological disorders (e.g., intrauterine adhesions, endometriosis, premature ovarian insufficiency), cardiovascular diseases, liver fibrosis, neurodegenerative diseases, diabetes, and even severe COVID-19. Recent advances highlight the therapeutic promise of MenSC-derived extracellular vesicles (EVs) and exosomes as cell-free therapies, as well as novel strategies such as gene editing and engineered delivery platforms. Despite these advances, challenges remain regarding standardization, donor variability, long-term safety, and clinical translation. Ongoing research aims to address these gaps and unlock the full therapeutic potential of MenSCs for future regenerative medicine applications.

II. NEED OF THE STUDY

More than 60% of stem-cell therapies worldwide still rely on invasive sources like bone marrow, even though these procedures can be painful, risky, and difficult to scale. At the same time, menstrual blood—a renewable, non-invasive source produced by millions every month—remains almost entirely overlooked in regenerative research. This gap highlights the need to study menstrual blood–derived stem cells (MenSCs), especially as global medicine shifts toward safer and more ethical cell-based therapies. Cultural stigma around menstruation, particularly in countries like India, further contributes to the scientific neglect of this promising resource. Understanding MenSCs can help researchers evaluate a stem-cell source that is easily accessible, less invasive, and potentially transformative for regenerative medicine. This study aims to clarify their therapeutic value and encourage broader scientific attention toward an underutilized but highly promising biological material.

III. METHODS

A systematic literature search was conducted to identify studies investigating the mechanisms, therapeutic applications, and future directions of MenSCs. Databases searched included PubMed, Web of Science, and Scopus, covering publications up to 2024. Search terms included "menstrual blood-derived stem cells," "MenSCs," "regenerative medicine," "mechanisms," "therapeutic applications," and "clinical trials." Both preclinical and clinical studies were included, as well as reviews and meta-analyses. Studies were screened for relevance based on titles and abstracts, followed by full-text review. Data extraction focused on MenSCs' biological properties, mechanisms of action (differentiation, immunomodulation, paracrine effects, homing), disease models, therapeutic outcomes, and reported limitations. Special attention was given to studies addressing cell-free therapies (e.g., exosomes), donor variability, and safety concerns. Discrepancies in study selection and data extraction were resolved by consensus among reviewers. The review adheres to PRISMA guidelines for systematic reviews.

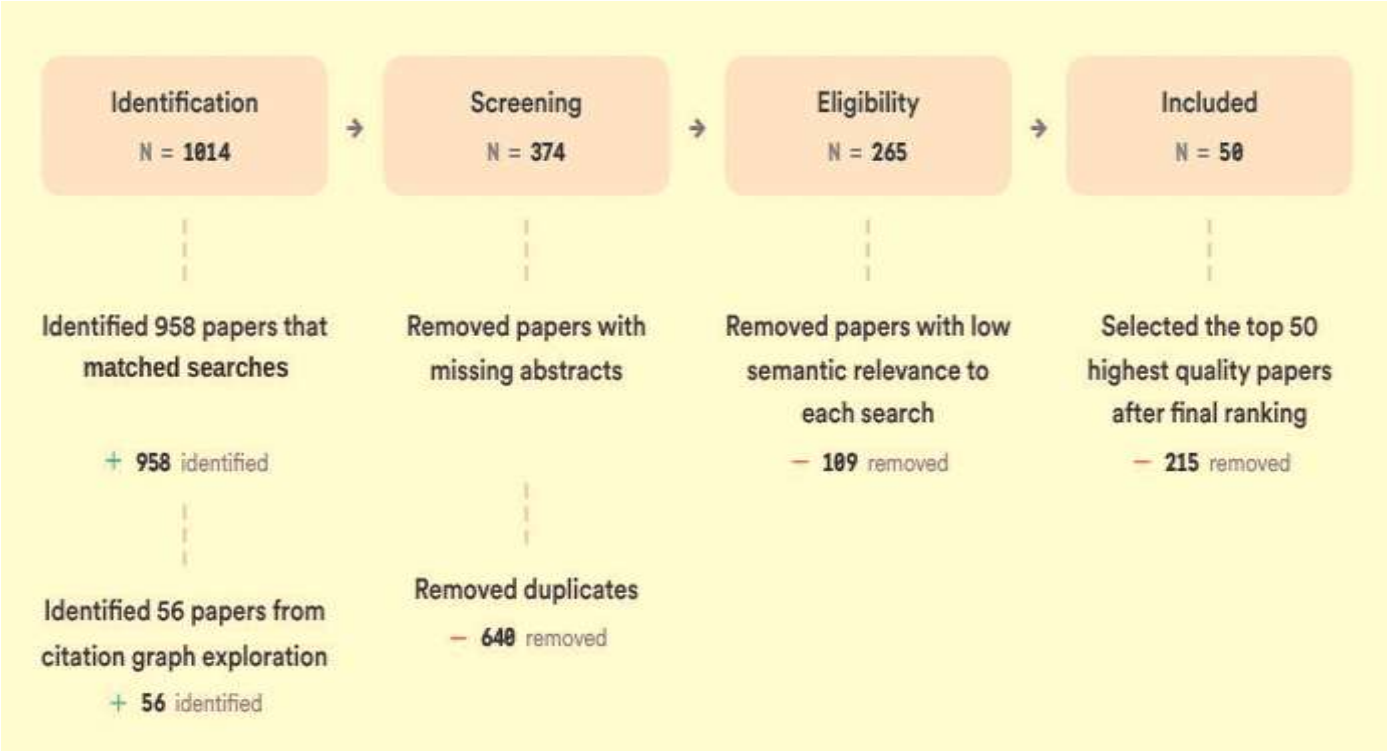

Figure 1. Summary of the systematic review process and study identification criteria.

IV. RESULTS

4.1 Biological mechanisms

Menstrual blood-derived stem cells (MenSCs) possess a unique biological profile that underpins their therapeutic versatility. These cells are characterized by a dual expression of mesenchymal and embryonic markers, such as CD44, CD166, and SSEA-4, which distinguishes them from other adult stem cell sources and endows them with robust proliferative and differentiation capacities. MenSCs are capable of differentiating into multiple lineages, including osteogenic, adipogenic, chondrogenic, neurogenic, and even germ cell-like phenotypes, reflecting their plasticity and potential for tissue regeneration in diverse contexts. A defining feature of MenSCs is their pronounced immunomodulatory activity. They interact with a variety of immune cells, including T cells, NK cells, and macrophages, and secrete anti-inflammatory cytokines such as IL-10 and TGF-β, which help modulate immune responses and create a regenerative microenvironment. This immunomodulation is particularly relevant in conditions characterized by chronic inflammation or autoimmunity. Additionally, MenSCs exert significant paracrine effects by releasing a spectrum of growth factors, cytokines, and extracellular vesicles (EVs), including exosomes. These secreted factors promote angiogenesis, inhibit apoptosis, and stimulate endogenous repair mechanisms in damaged tissues.

MenSCs also demonstrate a strong homing ability, migrating to sites of injury where they can engraft and participate in tissue repair. Notably, their secretome can influence local cell behavior and matrix remodeling, as seen in models of endometrial injury and liver fibrosis, where MenSCs modulate signaling pathways such as FAK/AKT and TGF-β/JNK to reduce fibrosis and enhance regeneration. Their immune-privileged status and low tumorigenic risk further support their safety profile for clinical applications.

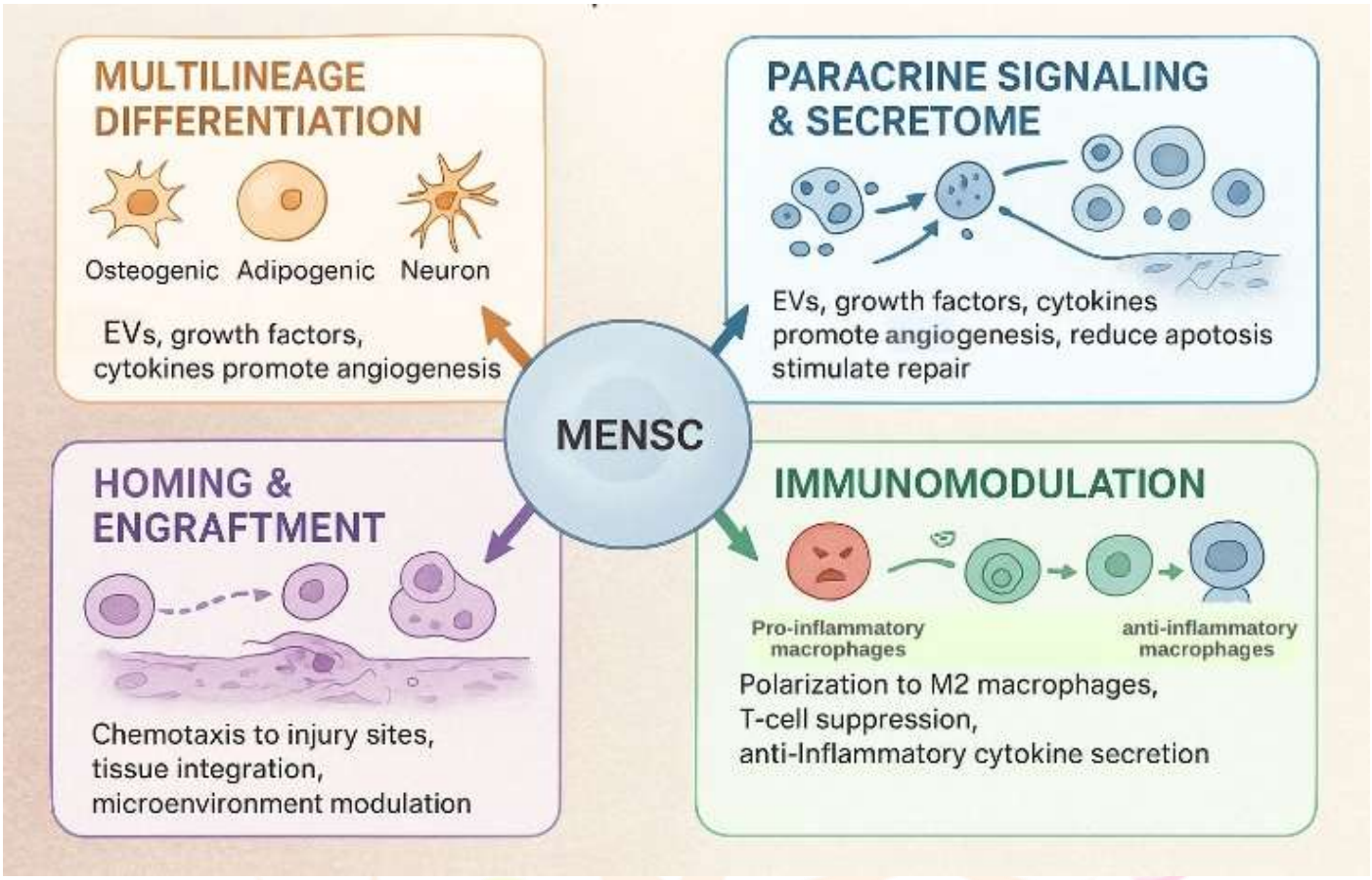

Figure 2. Schematic overview of the primary therapeutic mechanisms of Menstrual Blood-Derived Stem Cells (MenSCs). MenSCs contribute to tissue repair through 1) the paracrine secretion of growth factors, cytokines, and extracellular vesicles; 2) modulation of immune cell activity to reduce inflammation; 3) active homing to sites of tissue injury; and 4) differentiation into multiple mesenchymal lineages.

4.2 Therapeutic Application

The therapeutic applications of MenSCs span a wide spectrum of diseases, with both preclinical and early clinical studies demonstrating their efficacy. In gynecological disorders, MenSCs have shown the ability to restore endometrial function in models of Asherman syndrome and intrauterine adhesions, leading to improved endometrial thickness, reduced fibrosis, and enhanced fertility outcomes. In cases of premature ovarian insufficiency and ovarian senescence, MenSCs and their exosomes have been shown to inhibit granulosa cell apoptosis, promote angiogenesis, and activate protective signaling pathways, thereby preserving ovarian reserve and function.

Beyond reproductive health, MenSCs have demonstrated therapeutic benefits in non-gynecological conditions. In models of liver fibrosis, MenSCs migrate to injured hepatic tissue, where they suppress hepatic stellate cell activation and secrete antifibrotic mediators, resulting in improved liver function and reduced collagen deposition. In cardiovascular disease, MenSCs contribute to myocardial repair by promoting angiogenesis and reducing inflammation, while in neurological disorders such as stroke and Alzheimer's disease, they exert neuroprotective effects through anti-inflammatory and trophic mechanisms.
MenSC-derived extracellular vesicles are emerging as a promising cell-free therapy, delivering microRNAs and proteins that modulate disease pathways in conditions like endometriosis, pulmonary fibrosis, and diabetes. Early clinical reports also suggest safety and potential efficacy in treating conditions such as multiple sclerosis and heart failure, though larger trials are needed. The versatility, accessibility, and safety of MenSCs position them as a valuable tool in regenerative medicine, with ongoing research aimed at optimizing their therapeutic use across a growing range of indications.

4.3 Comparison with other stem cell sources

Compared to other mesenchymal stem cell (MSC) sources, menstrual blood-derived stem cells (MenSCs) demonstrate several distinct advantages and some limitations relevant to regenerative medicine. MenSCs are collected non-invasively and can be obtained repeatedly from healthy women, unlike bone marrow-derived MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs), which require invasive procedures for harvest. This ease of access allows for rapid expansion and the collection of sufficient cells for therapeutic use at lower passages. MenSCs also show a higher proliferation rate and greater colony-forming efficiency than BM-MSCs, with studies reporting a 2- to 4-fold increase in progenitor frequency and faster in vitro expansion.

Functionally, MenSCs share a similar immunophenotype and multilineage differentiation potential with BM-MSCs and AD-MSCs, but they exhibit superior migration and angiogenic properties. For example, MenSCs secrete higher levels of angiogenic factors such as VEGF and bFGF, and their conditioned media promote more robust angiogenesis in vitro and in vivo compared to BM-MSCs. Additionally, MenSCs have demonstrated a unique ability to support hematopoietic stem cell expansion more effectively than BM-MSCs. In terms of safety and immunogenicity, MenSCs are immune-privileged and have not shown tumorigenic potential in preclinical studies, similar to other MSC sources. However, MenSCs may be affected by donor-related

factors such as age and hormonal status, which can influence their proliferation and function.

In summary, MenSCs offer practical and biological advantages over traditional MSC sources, particularly in accessibility, proliferation, and angiogenic potential, though further standardization and clinical validation are needed.

Feature	MenSCs	Bone marrow MSCs(BM-MSCs)	Adipose MSCs(AD-MSCs)
Collection Method	Non-invasive (Menstrual Cup)	Invasive (Bone Aspiration)	Surgical (Liposuction)
Proliferation Rate	**High** (2-4x BM-MSCs)	Moderate (Senescence issues)	Good
Angiogenic Potential	**High** (VEGF, bFG rich)	Moderate	Moderate
Immunomodulatory Strength	**Strong** (IL-10, TGF-β)	Moderate	Moderate
Key Advantage	Accessibility & Proliferation	Established history	High cell yields per harvest

Table 1. Comparative profile of MenSCs against traditional mesenchymal stem cell sources.

4.4 Emerging strategies and future directions

Emerging strategies for menstrual blood-derived stem cell (MenSC) therapy focus on enhancing therapeutic efficacy, safety, and clinical translation. One major direction is the use of CRISPR/Cas9-mediated gene modification to improve MenSC function and disease-targeting abilities, potentially allowing for correction of genetic defects or enhancement of regenerative properties. Another rapidly advancing area is cell-free therapy using MenSC-derived exosomes and extracellular vesicles, which deliver bioactive molecules to target tissues and have shown promise in preclinical models for conditions such as liver failure, pulmonary fibrosis, ovarian regeneration, and endometriosis. These cell-free approaches may reduce risks associated with cell transplantation and simplify storage and delivery.

Precision medicine is also being pursued through single-cell RNA sequencing, which helps characterize MenSC heterogeneity and tailor therapies to individual patient profiles. Engineered MenSC-based therapies, including the use of biomaterial scaffolds and delivery platforms, are being developed to improve cell retention, survival, and integration at injury sites. Additionally, optimizing the stem cell niche and microenvironment is recognized as important for maximizing MenSC therapeutic outcomes.

Despite these advances, several challenges remain. Donor age, cell dose, transplantation route, and monitoring time can all influence therapeutic results. There is a need for standardized protocols for MenSC isolation, culture, and characterization, as well as rigorous clinical trials to establish long-term safety and efficacy. Regulatory oversight is expected to become more stringent as MenSC therapies move toward broader clinical application. Overall, combining traditional approaches with these novel strategies is anticipated to expand the clinical potential of MenSCs in regenerative medicine.

V. DISCUSSION

The literature consistently demonstrates that MenSCs are a highly promising source of stem cells for regenerative medicine, offering unique advantages over traditional sources such as bone marrow and adipose tissue. Their mechanisms of action—differentiation, immunomodulation, paracrine signaling, and homing—are well-supported by both in vitro and in vivo studies. The breadth of therapeutic applications, from gynecological to non-gynecological diseases, underscores their versatility.

However, challenges remain. The lack of standardized protocols for MenSC isolation, culture, and characterization introduces variability and complicates clinical translation. Donor heterogeneity, age, hormonal status, and environmental factors can affect MenSC properties and therapeutic efficacy. Long-term safety data are limited, and more rigorous clinical trials are needed to establish efficacy and monitor for adverse effects.

Emerging strategies such as gene editing, engineered delivery systems, and cell-free therapies using MenSC-derived EVs offer exciting avenues for overcoming current limitations and expanding clinical applications. The field is rapidly evolving, with

ongoing research addressing mechanistic questions, optimizing protocols, and exploring new therapeutic targets.

Claim	Evidence Strength	Reasoning
MenSCs are a safe, non-invasive, and abundant source of MSCs for regenerative medicine	Strong	Multiple studies confirm high proliferation, low immunogenicity, and lack of ethical issues
MenSCs exert therapeutic effects via differentiation, immunomodulation, paracrine signaling, and homing	Strong	Mechanistic studies and animal models support these actions
MenSCs are effective in preclinical models for gynecological and non-gynecological diseases	Moderate	Animal and early clinical studies show efficacy in diverse conditions
MenSC-derived EVs/exosomes offer promising cell-free therapeutic options	Moderate	Preclinical studies demonstrate efficacy and safety, but clinical data are limited
Standardization and long-term safety of MenSC therapies remain unresolved	Moderate	Variability in protocols and limited long-term clinical data
The clinical efficacy of MenSCs in large-scale, long-term human trials is not yet established	Weak	Few clinical trials, small sample sizes, and short follow-up

Figure 3. Key claims and support evidence identified.

VI. CONCLUSION

Menstrual blood-derived stem cells represent a unique, versatile, and promising tool for regenerative medicine, with demonstrated efficacy in preclinical models and early clinical studies. Their mechanisms of action, broad therapeutic potential, and ease of collection position them as a valuable alternative to traditional stem cell sources. However, challenges related to standardization, donor variability, and long-term safety must be addressed to fully realize their clinical potential.

6.1 Research Gaps

Despite significant progress, research gaps remain in standardization of MenSC protocols, long-term safety, large-scale clinical efficacy, and mechanistic understanding in specific disease contexts.

Disease/Application	Preclinical Models	Clinical Trials	EV/Exosome Studies	Standardization Studies	Long-term Safety
Gynecological disorders	12	4	3	2	1
Non-gynecological diseases	10	2	2	1	GAP
Mechanistic studies	8	GAP	4	2	GAP
Cell-free therapies	5	1	7	1	GAP
Standardization/safety	2	GAP	1	5	2

Figure 4. Matrix showing research coverage and gaps by disease/application and study attribute.

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