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Review

Mesenchymal stem cell secretome: A promising therapeutic strategy for erectile dysfunction?

Ria Margiana [a,b,c,d,e,f,*], Younes Pilehvar [g], Fatkhurrohmah L. Amalia [c,d,h], Silvia W. Lestari [b,e,f,i], Supardi Supardi [c,d], Reny I'tishom [c,j,*]

[a] *Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[b] *Master's Programme Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[c] *Andrology Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*
[d] *Dr. Soetomo General Academic Hospital, Surabaya, Indonesia*
[e] *Indonesia General Academic Hospital, Depok, Indonesia*
[f] *Ciptomangunkusumo General Academic Hospital, Jakarta, Indonesia*
[g] *Cellular and Molecular Research Center, Cellular and Molecular Medicine Research Institute, Urmia University of Medical Science, Urmia, Iran*
[h] *Dr. Kariadi Hospital, Semarang, Indonesia*
[i] *Department of Medical Biology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[j] *Department of Biomedical Science, Faculty of Medicine, Universitas Airlangga Surabaya, Indonesia*

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Abstract *Objective:* The secretome, comprising bioactive chemicals released by mesenchymal stem cells (MSCs), holds therapeutic promise in regenerative medicine. This review aimed to explore the therapeutic potential of the MSC secretome in regenerative urology, particularly for treating erectile dysfunction (ED), and to provide an overview of preclinical and clinical research on MSCs in ED treatment and subsequently to highlight the rationales, mechanisms, preclinical investigations, and therapeutic potential of the MSC secretome in this context.
Methods: The review incorporated an analysis of preclinical and clinical research involving MSCs in the treatment of ED. Subsequently, it delved into the existing knowledge regarding the MSC secretome, exploring its therapeutic potential. The methods included a comprehensive examination of relevant literature to discern the processes underlying the therapeutic efficacy of the MSC secretome.

* Corresponding author. Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia (R. Margiana); Andrology Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia (R. I'tishom).
E-mail address: ria.margiana@ui.ac.id (R. Margiana), ritishom@fk.unair.ac.id (R. I'tishom).
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Results: Preclinical research indicated the effectiveness of the MSC secretome in treating various models of ED. However, the precise mechanisms of its therapeutic efficacy remain unknown. The review provided insights into the anti-inflammatory, pro-angiogenic, and trophic properties of the MSC secretome. It also discussed potential advantages, such as avoiding issues related to cellular therapy, including immunogenicity, neoplastic transformation, and cost.
Conclusion: This review underscores the significant therapeutic potential of the MSC secretome in regenerative urology, particularly for ED treatment. While preclinical studies demonstrate promising outcomes, further research is essential to elucidate the specific mechanisms underlying the therapeutic efficacy before clinical application. The review concludes by discussing future perspectives and highlighting the challenges associated with the clinical translation of the MSC secretome in regenerative urology.

1. Introduction

Sexual function and the ability to maintain an erection are impacted by the disorder known as erectile dysfunction (ED). This disorder can be caused by a variety of factors, but common culprits include nerve and blood flow damage [1]. Hence, in order to address ED, it is necessary to utilize a treatment approach that promotes the growth of blood vessels, protects nerves, and encourages regeneration. Numerous medications have been utilized to treat this condition, with phosphodiesterase type-5 inhibitors being commonly prescribed by medical professionals [2]. Nonetheless, it is recognized that the curative impact of these inhibitors is limited due to adverse reactions, such as the relaxation of smooth muscles and the buildup of collagen [3]. In recent times, the use of stem cell technology has acquired significant interest as a potential solution to address the challenges associated with treating ED [4]. Stem cell therapy necessitates the introduction of millions of cells to overcome the low engraftment rate *in vivo*, but this approach also carries the risk of tumor development. Moreover, the storage and cultivation of cells entail lengthy preparation time and significant expenses, while an immune response is also a potential concern [5].

Researchers are increasingly focusing on the development of mesenchymal stem cell (MSC) secretome, which involves utilizing cytokines and trophic factors secreted from cells, to address the limitations of stem cell therapy [3]. The MSC secretome treatment method offers the benefit of utilizing the paracrine action of stem cells while eliminating the potential for tumor formation. Additionally, MSC secretome therapy has minimal immune response and serves as a readily available solution because the MSC secretome can be preserved after production [6].

Therefore, in this review, we discuss the preclinical and clinical research of MSCs in the treatment of ED, and then the rationales, mechanisms, preclinical investigations, and therapeutic potential of MSC secretome in treating ED will be highlighted. Finally, we describe the future perspectives and hurdles in the clinical translation of MSC secretome.

2. ED, pathophysiology, risk factors, and current treatment options

ED, defined as the persistent inability to achieve and maintain a satisfactory erection, is a common issue affecting about 30 million American men [7]. It is closely linked to the neurovascular processes involving the endothelium and smooth muscle cells in the corpus cavernosum. When stimulated, nitric oxide (NO) and acetylcholine play vital roles in achieving an erection by relaxing smooth muscles and reducing intracellular Ca^{2+} levels. Various factors, such as cavernous nerve injury (CNI) or hypoxia, can interfere with these mechanisms, leading to veno-occlusive dysfunction [8,9].

Multiple risk factors, including smoking, obesity, sedentary lifestyle, alcohol consumption, and thyroid disorders, contribute to ED by causing hormonal imbalances and endothelial dysfunctions [10].

Conditions like hypertension, dyslipidemia, diabetes, and depression also increase susceptibility to ED [11]. Medications, particularly antihypertensives, antidepressants, and antipsychotics, may cause up to 25% of ED cases, with specific drugs being associated with this condition [12].

Notably, ED is interconnected with cardiovascular and metabolic diseases, as it can increase the risk of developing these conditions. Research suggests that ED often precedes cardiovascular events and is associated with other issues such as early ejaculation and urinary tract symptoms [10,13].

Treatment options for ED include seeking help from mental health professionals, lifestyle changes, oral medications, and more invasive procedures like vacuum constriction devices, intracorporal injections, and surgical penile prostheses [14]. While oral phosphodiesterase type-5 inhibitors are commonly recommended due to their effectiveness and safety, they may not work for all patients and only provide temporary relief without addressing the underlying cause [15]. New minimally invasive therapies like MSCs-based treatments are being explored to meet the unmet needs in treating ED.

3. Stem cell technology: potential of MSCs in treating ED

The potential for stem cell therapy in regenerative urology has been opened by advances in stem cell research. Stem cells are distinctive because they can self-renew, proliferate limitlessly, and differentiate into different terminal cell types. Additionally, stem cells have unique properties such as pro-angiogenic, antifibrotic, and anti-apoptotic, which could enhance the treatment of urological diseases that lack surgical or pharmacological therapies [16,17].

These versatile cells can be categorized into different types based on their differentiation potential: (i) totipotent stem cells—these are exemplified by the zygote, which has the unique ability to give rise to any cell type within an organism, including extraembryonic structures; (ii) pluripotent stem cells—embryonic stem cells fall into this category, as they can differentiate into any cell within the germ layers, giving rise to a wide variety of cell types; (iii) multipotent stem cells—these stem cells have the capacity to differentiate into various cell types within specific lineages, and an example is hematopoietic stem cells (HSCs), which can give rise to different types of blood cells; (iv) oligopotent stem cells—these stem cells can differentiate into only a limited range of cell types, not as diverse as multipotent or pluripotent stem cells; and (v) unipotent stem cells—these stem cells have a highly restricted differentiation potential and give rise to a specific cell type [18].

In adults, a variety of multipotent, oligopotent, and unipotent stem cells are distributed throughout the body. These adult stem cells play a crucial role in maintaining tissue homeostasis and promoting tissue regeneration. Some well-known examples include MSCs, HSCs, neural stem cells, and dermal stem cells.

For ethical reasons, the focus of clinical applications of stem cells is primarily on adult stem cells. Fortunately, scientific advancements have made it possible to generate pluripotent stem cells from adult somatic cells through genetic reprogramming. These reprogrammed cells are known as induced pluripotent stem cells and share many characteristics with embryonic stem cells [19,20].

Among various types of stem cells, HSCs have been extensively studied for over five decades. They can be isolated from various sources, including bone marrow, peripheral blood, or umbilical cord blood. The isolation and standardization of HSCs, as well as their use in cell therapy, have been well-established. HSCs are primarily employed in transplantation procedures for patients with a compromised hematopoietic system, which can be caused by various medical conditions, such as leukemia or anemia [21].

MSCs have emerged as a highly studied and versatile type of stem cell with immense potential for regenerative medicine applications. First identified by Friedenstein et al. [22] in 1970 in guinea-pig bone marrow and spleen, MSCs were initially described as fibroblastic cells with the ability to differentiate into osteoblasts [23]. Further research revealed their capacity to differentiate into a wide array of cell types, including adipocytes, chondrocytes, hepatocytes, and neurons, spanning multiple germ layers [24,25]. MSCs can be sourced from various tissue, such as bone marrow, adipose tissue, and umbilical cord, and must undergo expansion and characterization according to the International Society for Cell Therapy guidelines. The International Society for Cell Therapy has defined specific criteria that MSCs must meet, including plastic adherence, expression of cluster of differentiation 73 (CD73), CD90, and CD105 surface markers, and the absence of certain markers. Additionally, MSCs must demonstrate their *in vitro* differentiation potential [26].

The therapeutic potential of MSCs is driven by several key attributes, making them valuable for treating various conditions [27]. Firstly, these cells possess immunomodulatory activity, allowing them to regulate immune responses and reduce inflammation, which is beneficial in the treatment of immune-related disorders. Additionally, MSCs have the capability to differentiate into multiple cell types, contributing to tissue regeneration. They can be easily isolated from their source and expanded in culture, ensuring a scalable supply for therapy [28]. Moreover, they are amenable to cryopreservation, allowing long-term storage without compromising viability. Furthermore, MSCs are hypoimmunogenic, expressing low levels of major histocompatibility complex class I and class II, thus minimizing the risk of immune rejection upon transplantation. They can be administered intravenously, enabling systemic delivery, and are actively involved in producing and secreting paracrine factors with regenerative potential [29,30].

To effectively utilize MSCs in clinical practice, it is essential to have a comprehensive understanding of their therapeutic actions. Recent research has uncovered the intricate nature of MSC actions. These cells have demonstrated an exceptional ability to migrate towards areas of injury, often in response to cytokine gradients. While some MSCs may attach to injured tissue, undergo changes, and integrate with host tissues, their therapeutic benefits go beyond these processes [31,32].

In recent years, the paracrine theory of stem cell activity has gained prominence. It emphasizes that MSCs exert a significant therapeutic influence primarily through the secretion of bioactive paracrine substances collectively referred to as the secretome. This secretome comprises factors with antifibrotic, pro-angiogenic, and anti-apoptotic properties, playing a pivotal role in tissue repair and regeneration.

This understanding has paved the way for the clinical utilization of MSC products, including their secretome, which can be derived from various tissue sources. Historically, bone marrow-derived MSCs (BM-MSCs) dominated the clinical landscape until around 2008. However, there has been a notable shift in clinical practice, with equal usage of MSC products derived from bone marrow, adipose tissue, and placental tissue. Each tissue source comes with its own unique clinical safety and efficacy profiles [33].

Notably, recent insights suggest that the direct injection of cell-derived secretome may offer advantages in terms of safety when compared with the infusion of whole cells. This is particularly relevant due to the highly variable procoagulant nature of MSCs, notably their expression of tissue factor. The expression of tissue factor can trigger the instant-blood-mediated inflammatory reaction upon systemic infusion, which carries the risk of clot formation, thrombus, and ischemia in small vessels [34,35]. This

consideration is crucial in various clinical applications, including the potential use for conditions such as ED. Therefore, understanding the differential effects and safety profiles of MSC products and their secretome from distinct tissue sources is paramount for harnessing their full therapeutic potential.

3.1. Stem cell therapy of ED: preclinical investigations

In 2004, Bochinski et al. [36] injected embryonic stem cells into rats with ED caused by CNI. Since then, various investigations have explored the efficiency of stem cell treatment for ED brought on by factors such as aging, diabetes, hyperlipidemia, and CNI. In pre-clinical animal models, the stem cell kinds that have been most studied are MSCs, embryonic stem cells, endothelial progenitor cells, and neural crest stem cells [37,38].

A meta-analysis conducted by Hou and colleagues [39] in 2017 assessed 20 studies involving 248 rats and found that adipose tissue-derived MSCs (AT-MSCs) therapy was effective in repairing cavernous tissue. The study also revealed that AT-MSCs modified growth factors such as nerve growth factor, vascular endothelial growth factor (VEGF), hepatocyte growth factor, and neurotrophic factors like brain-derived neurotrophic factor, which resulted in a considerable improvement in erectile function in comparison with using AT-MSCs alone. Additionally, a considerable improvement was seen in models of ED in diabetic rats when a large number of cells ($>1\times10^6$), insulin therapy, or hypoxic preconditioning of AT-MSCs were used.

Recently, researchers have surveyed ways to improve the therapeutic effectiveness of stem cells through modifications in their preparation or through co-interventions. For instance, He et al. [40] explored the application of AT-MSCs that were co-modified with mothers against decapentaplegic homolog 7 (Smad7) and VEGF in a CNI rat model. They found that rats treated with these co-modified AT-MSCs showed greater improvements in their erectile function.

Zhuang et al. [41] conducted a study on urine-derived MSCs and discovered that administering them in hyaluronic acid vesicles had better results for diabetic rats than just urine-derived MSCs administration. This suggests that using hyaluronic acid with other stem cells may also lead to improved outcomes, and it can be applied topically, which is advantageous in terms of treatment discomfort. Additionally, researchers have tried other methods to enhance stem cell therapy for ED, such as using hydrogels and growth factor-coated membranes for physical administration in preclinical models.

3.2. Stem cell therapy of ED in the clinical setting

A summary of 23 interventional trials that have been filed in ClinicalTrials.gov since 2010 and those sought to determine the safety and efficacy of stem cell therapy for treating ED are shown in Table 1. Among these, nine studies have been finalized and their key features, outcomes, interventions, and results are outlined [42—50]. Although MSCs generated from the placenta and umbilical cord have also been employed, BM-MSCs and AT-MSCs are the chief sources of stem cells used for therapeutic purposes in humans. Direct intracavernous injection (ICI) as the main method of cell delivery was employed in the majority studies. The protocols have generally followed a similar approach, which involves isolating the desired stem cells from either the healthy donor's fat or bone marrow tissue in the case of allogeneic transplantation or from patients in autologous transplantation. Before being employed either directly by injection into the target patient or through the application of stromal vascular factor, which is derived from the isolated stem cells, the isolated clonal cells are normally grown through *in vitro* culture.

Most studies, which primarily consisted of preliminary phase I/II clinical trials, focused on evaluating the safety and tolerability of MSC treatment for ED. Overall, these studies did not report any significant harmful effects resulting from the administration of MSCs.

In 2010, Bahk et al. [42] conducted the first human clinical trial to use allogeneic umbilical cord MSCs for treating ED for patients with diabetes mellitus. The trial involved seven men between the ages of 57 years and 83 years who received an ICI of 1.5×10^7 cells. Within 1 month, most of the patients regained morning spontaneous erections, and these results persisted for 6 months of follow-up. After 2 weeks of treatment start, it was also detected a decrease in blood glucose levels, indicating a potential benefit of MSCs in treating diabetes. The safety profile of the treatment was evaluated in a subsequent clinical trial by Levy et al. [43]. This trial followed eight patients who had complete ED that did not respond to phosphodiesterase inhibitors treatment for 6 months. The study analyzed the adverse effects of treatment and the functional and hemodynamic results following injecting placenta-derived stem cells (PSCs). There were no severe adverse effects noted, and the mean penile arterial flow improved and remained better for 6 months after therapy began.

A clinical trial called the INSTIN study, conducted by Yiou et al. [44,45], involved 18 patients (12 in the first phase) who had undergone radical prostatectomy. The study used increasing doses of the ICI of BM-MSCs. The authors found that a single ICI of autologous BM-MSCs was both effective and safe in treating vasculogenic ED. At the 6-month follow-up, patients reported improved erectile function and sexual satisfaction, which persisted for 1 year. During long-term follow-up, no treatment-related adverse effects were observed. However, there was a slight decline in erectile function compared to the outcomes gained in the first-year treatment. It was suggested that a further ICI might be necessary to maintain the therapeutic effect over time.

Al Demour et al. [46] conducted clinical trials on diabetic patients to investigate the application of autologous BM-MSCs and allogenic Wharton's jelly stem cells for treating erectile function. It was found that the ICI of BM-MSCs was both effective and safe, resulting in significant improvements in the International Index of Erectile Function-15 (IIEF-15) and erection hardness scale questionnaires [46]. Then, the application of two consecutive ICIs of Wharton's jelly stem cells for the first time in 22 diabetic patients with erectile function showed positive

Table 1 MSC therapy of ED in the clinical trials.

Study	Study design	Cell type	Comorbidity	Administration; dose route	Patient, *n*; FU, month
Fode et al., 2023 [55]	Prospective case series	AT-MSCs	Chronic organic ED	Single ICI; unquantified	10; 6
Koga and Horiguchi, 2022 [59]	Open label and pilot	SHED-CM	Chronic organic ED	3–8 ICI; unquantified	38; 8
Mirzaei et al., 2021 [58]	Randomized single-blinded	Oral mucosa-MSCs	T2DM	Single ICI; (50–60) $\times 10^6$ cells	20; 6
You et al., 2021 [100]	Phase I open label	BM-MSCs	Post-prostatectomy ED and T2DM	Single ICI; 30×10^6 cells	10; 12
Al Demour et al., 2021 [51]	Phase I open label	WJ-MSCs	T2DM	Two ICIs; 20×10^6 cells	22; 12
Bieri et al., 2020 [49]	Phase I dose escalation	ABMC	Chronic organic ED	Two ICIs; 3 mL or 6 mL dose group (10^8 cells)	40; 12
Zasieda, 2020 [57]	Prospective cohort	MSC-DEs	Metabolic syndrome	6 ICIs; 5 mL	38; 3
Protogerou et al., 2020 [48]	Phase I open label pilot	AT-MSCs and PL	T2DM, hypertension, hypercholesterolemia, and Peyronie disease	Single ICI; 47×10^6 cells	5; 6
Ory et al., 2020 [56]	Retrospective cohort	Transendocardial hMSCs	Cardiomyopathy-ED	Single ICI; 2×10^8 cells	36; 12
Protogerou et al., 2019 [54]	Open label pilot	AT-MSCs and PL	T2DM, hypertension, hypercholesterolemia, and peyronie disease	Single ICI; 47×10^6 cells	8; 3
Al Demour et al., 2018 [46]	Phase I open label	BM-MSCs	T2DM	Two ICIs; 30×10^6 cells	4; 12–24
Haahr et al., 2016 [47]	Phase I open label	AT-MSCs	Post-radical prostatectomy	Single ICI; (8.4–37.2) $\times 10^6$ cells	17; 6
Haahr et al., 2018 [50]	Phase I open label	AT-MSCs	Post-radical prostatectomy	Single ICI; (8.4–37.2) $\times 10^6$ cells	21; 12
Yiou et al., 2016 [45]	Phase I	BM-MNCs	Post-radical prostatectomy	Single ICI; 2×10^7 -2×10^9 cells	12; 12
Yiou et al., 2017 [44]	Phases II	BM-MNCs	Post-radical prostatectomy	Single ICI; 10×10^8 cells	18; 62.1
Levy et al., 2016 [43]	Phase I-II open label	PM-MSCs	Chronic organic ED	Single ICI; unquantified	8; 6
Garber and Carlos, 2015 [53]	Pilot study	AT-MSCs	T2DM	Single ICI; 1.5×10^7 cells	6; 12
Ichim et al., 2013 [101]	Case report	BM-MSCs	Chronic organic ED	Single ICI; unquantified	1; 18
Bahk et al., 2010 [42]	Phase I pilot study, single blinded	UC-MSCs	T2DM	Single ICI; 1.5×10^7 cells	7; 9

ABMC, autologous bone marrow concentrate; MSCs, mesenchymal stem cells; AT-MSCs, adipose tissue-derived MSCs; BM-MSCs, bone marrow-derived MSCs; ED, erectile dysfunction; FU, follow-up; hMSCs, human MSCs; ICI, intracavernosal injection; MSC-DEs, MSC-derived exosomes; PL, platelet lysate; PM-MSCs, placental matrix-derived MSCs; SHED-CM, stem cells from human exfoliated deciduous teeth-conditioned medium; T2DM, type 2 diabetes mellitus; UC-MSCs, umbilical cord-derived MSCs; WJ-MSCs, Wharton's jelly-MSCs.

outcomes at the 12-month follow-up, with improvements in efficacy, safety, and tolerability determined through erection hardness scale, IIEF-15 questionnaires, and deep pelvic endometriosis imaging [51].

As previously mentioned, adipose tissue is another commonly studied source of MSCs for treating erectile function. AT-MSCs are cells that play a key function in revascularizing damaged tissue, inhibiting apoptosis, and modulating the immune system. They possess similar regenerative and multipotent capabilities as BM-MSCs but are easier to obtain in large quantities. Additionally, they have a significant paracrine effect due to their secretion of extracellular matrix components, growth factors such as VEGF and basic fibroblast growth factor, and numerous cytokines, all of which have antiapoptotic and angiogenic properties [52].

A clinical trial conducted by Garber and Carlos [53] in 2015 involved injecting 1.5×10^7 AT-MSCs into six diabetic patients. The AT-MSCs were acquired after culturing. Within a month, four out of the six patients regained spontaneous morning erections and were able to engage in sexual intercourse for up to 12 months after the ICI with the

help of phosphodiesterase inhibitor treatment during the last month. These findings are consistent with the work conducted by Haahr and colleagues [47], who showed that the ICI of autologous AT-MSCs was safe and reliable for treating patients' ED after radical prostatectomy. The results of the IIEF-15 scoring significantly enhanced at 6 months after treatment, and this improvement sustained at 12 months. No adverse events were noted during the 12-month follow-up. It is interesting that this improvement was seen in patients who were included in the study with normal preoperative erectile function and urine continence. The working group is conducting a phase III study with a larger sample of post-prostatectomy patients. Meanwhile, Protogerou et al. [48,54] have developed a technique that combines AT-MSCs with substances found in stromal vascular factor. They administered cultured AT-MSCs suspended in platelet lysate plasma and observed positive results in improving erectile function after 1, 3, and 6 months of follow-up, with no adverse side effects.

With the help of the myStem® X2 kit (Puremed, Roskilde, Denmark), a single-use kit for autologous stromal tissue graft preparation, Fode and co-workers [55] tested the viability and safety of a novel, minimally invasive technique for autologous AT-MSCs transplantation on a case series of 10 males. There were no adverse side effects noted, and the outcomes were comparable to the recent clinical studies using AT-MSCs [48,54].

While many studies have focused on stem cells isolated from adipose and bone marrow tissue, other strains of stem cells have also been explored. Ory et al. [56] conducted a retrospective research studying the impact of transendocardial human MSCs injection on ED in cardiomyopathy patients. Twenty million to 200 million of the cells, both autologous and allogeneic, were employed in the study. This investigation was the first to use randomized, placebo-controlled data to assess the impact of stem cell therapy on erectile function.

Zasieda [57] conducted a study that administered MSCs-derived exosomes intravenously for 6 weeks, once per week, along with a combination of MSCs-derived exosomes injection and low-intensity shock wave therapy twice per week, with 3 Hz frequency and 3000 strikes. Results revealed a dramatic enhance in the IIEF score in comparison with baseline, as well as improvements in peak systolic velocity and a reduction in end diastolic penile velocity post-therapy.

Mirzaei et al. [58] injected intracavernously stem cells derived from the oral mucosa at a dose of 50—60 million cells. According to the study, no side effects were reported, and the treatment enhanced both sexual function and the resistance index, as well as peak systolic velocity index of penile arteries in diabetic individuals.

In a study conducted by Koga and Horiguchi [59], to investigate the potential of cellular regeneration for enhancing sexual function in the ED patients, stem cells from human exfoliated deciduous teeth-conditioned medium (SHED-CM) were directly injected. The treatment was administered to 38 patients who had not undergone prior treatment with testosterone or phosphodiesterase type 5 inhibitor replacement treatment, and after three courses of SHED-CM treatment, there was a considerable enhancement in IIEF-5 scores. To precisely ascertain the effects of SHED-CM on vascular endothelial cells and its long-term influence, no pathological analysis was carried out. Despite this, SHED-CM therapy is safe and has the potential to restore corpora cavernosa vascular damage, making it a possible treatment for ED sufferers in the future.

The clinical studies conducted thus far have not explored the specific mechanisms through which stem cells improve ED. However, preclinical studies have shown that stem cells do not always differentiate during the repair process and that their therapeutic effects can continue even after their disappearance. Additionally, cell-free treatments like secretome have demonstrated regenerative advantages and are believed to be crucial to improve erectile function. The antiapoptotic, anti-inflammatory, proangiogenic, and antifibrotic effects of MSC secretomes have demonstrated potential in *in-vivo* models of ED and could be a hopeful treatment choice in the future. Compared to traditional cell-based therapies, MSC secretomes offer advantages such as safety and cost-effectiveness.

4. MSC secretome and its potential mechanism of action

The secretome of MSCs is made up of various soluble substances, including cytokines, hormones, growth factors, and lipid mediators [60]. These substances work together to generate an environment that is conducive to cellular regeneration. The secretome has been found to promote inflammatory and immune modulation, facilitate vascularization, and prevent apoptosis. Recent research proposes that some of these substances are contained within extracellular vesicles, such as microvesicles and exosomes, derived from MSCs, which allows for more effective communication and targeting than soluble substances alone [61].

The secretome of MSCs provides benefits for regenerative urology that surpass those of traditional cell-based therapies. Firstly, using the acellular secretome for therapy may avoid problems associated with maldifferentiation, immunoreactivity, and tumorigenicity that come with cell-based treatments [62]. Secondly, secretome therapy may allow for more cost-effective and effective developing off-the-shelf treatments compared to the maintenance and expansion of individualized cell populations. Lastly, The active components of the MSCs secretome may be altered and tailored to target particular disease processes once this is known [63].

4.1. Pro-angiogenic effects of MSC secretome

Angiogenesis, the process of creating new blood vessels from existing ones, is essential for the survival and tissue regeneration. This process provides nutrients and oxygen to the damaged area. MSC secretome contains a significant amount of VEGF, a key factor in angiogenesis, as well as other pro-angiogenic cytokines like basic fibroblast growth factor, placental growth factor, and monocyte chemoattractant protein-1. These cytokines have been demonstrated to help MSC secretome increase endothelial cell proliferation *in vitro*, and its efficiency is somewhat inhibited by anti-VEGF or anti-basic fibroblast growth factor antibodies. In a mouse model of hindlimb ischaemia, the infusion of MSCs enhanced blood flow, collateral formation,

and functional results. However, there was no proof that MSCs were integrated into the target tissue. The injection of MSC secretome also replicated these beneficial effects, while the control medium did not. This shows that a paracrine route, which may be replicated by therapy with just the secretions, was responsible for the therapeutic impact of MSCs [64,65].

4.2. Anti-inflammatory, immunosuppressive, and anti-fibrotic properties of MSC secretome

The immune system plays a vital function in fighting infections and regenerating damaged tissue, but excessive immune responses can be harmful. Examples include septic shock and heart remodeling after a heart attack. MSCs may help regulate these responses by converting activated macrophages to an anti-inflammatory state, hindering natural killer cell activation, suppressing dendritic cell function, and modulating T cell balance. MSCs achieve this through the secretion of factors such as transforming growth factor beta 1 (TGF-β1), prostaglandin E2, NO, interleukin 6, and indoleamine 2,3-dioxygenase. Therefore, potential therapeutic strategies for treating ED include targeting these pathways [65,66].

In humans, tissue injury typically results in scar formation rather than tissue regeneration, which is a process observed in some other organisms. However, there are some exceptions to this rule, such as the adult epidermis and liver, which have regenerative abilities. This is believed to be because of the presence of stem cells in these tissue that can either substitute damaged cells or release healing factors. These regenerative abilities are present during fetal development but are lost after birth [63].

In a similar way, MSCs may play a role in promoting tissue regeneration instead of scar formation in other organs after injury or surgery by releasing healing factors. Studies have revealed that MSCs can improve wound healing in mice by encouraging the movement of certain cells to the injured area through cytokines that have trophic and anti-inflammatory effects. Therefore, using MSC secretome as a treatment after surgery or trauma may help accelerate tissue regeneration and reduce fibrosis and scarring [67,68].

4.3. Anti-apoptotic effects of MSC secretome

Various investigations have shown that MSCs release biologically active substances that protect cells from damage and prevent cell death. These protective effects are likely due to the immune and blood vessel promoting properties of the MSCs' secretions, as well as their ability to directly prevent cell death [69]. Takahashi et al. [70] found platelet-derived growth factor and insulin-like growth factor-1, among other cytokines like interleukin-1β and VEGF, in the supernatant of MSCs. They demonstrated that these cytokines prevented cardiomyocyte apoptosis *in vitro* using terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assays. Additionally, intraperitoneal and intramyocardial injections of MSC supernatant improved contractile function in a rat model of myocardial ischemia. It was speculated that the enhanced effect from intraperitoneal injections may be due to the extra dose of cytokines or that intramyocardial injections of cytokines may have caused harm to the cardiac muscle tissue via anti-inflammatory properties. Li et al. [71] discovered that MSCs release substances that prevent alveolar macrophage apoptosis through transwell co-culture experiments. The expression of apoptosis regulator B-cell lymphoma 2-associated X protein (BAX) and pro-apoptotic proteins, such as caspase 3 were reduced while levels of anti-apoptotic protein apoptosis regulator B-cell lymphoma 2 were increased in alveolar macrophages. Fall et al. [72] showed that local injection of bone marrow mononuclear cells including MSCs partially restored erectile responses in a rat model of ED brought on by bilateral cavernous nerve ablation. This treatment augmented the expression of neuronal NO synthase (nNOS) and endothelial neuronal NO synthase (eNOS) while significantly decreasing the number of apoptotic cells in the erectile tissue. These preclinical studies suggest that the cytoprotective effect of MSCs could be applied in future therapies for ED.

4.4. MSC secretome for ED

At present, treatments for ED focus on augmenting blood flow to the penis through the application of drugs like phosphodiesterase inhibitors, intraurethral suppositories, or ICIs. In cases where these measures are unsuccessful, surgical implantation of a penile prosthesis may be necessary [63,73]. However, the therapeutic potential of MSCs, with their capability to promote nerve growth and blood vessel, has been proved in preclinical studies using animal models of ED, suggesting that they may offer a promising treatment option for men suffering from impotence in the future.

Albersen et al. [74] conducted a study using rats with bilateral CNI to simulate ED after radical prostatectomy. The rats were treated with the ICI of labelled AT-MSCs, AT-MSCs lysate, or phosphate-buffered saline immediately after injury. Intracavernous pressure was measured 4 weeks following electrostimulation of the distal cavernosal nerve to assess erectile function. The ratio of intracavernous pressure to mean arterial pressure was considerably superior in rats treated with AT-MSCs or its lysate than in those treated with controls, according to the data. Also, compared to control-treated rats, rats given AT-MSCs or AT-MSCs lysate showed more nNOS-positive nerve fibers, greater smooth muscle content preservation, and less fibrosis. Despite the fact that few labelled stem cells were found in the cavernosal tissue of animals treated with AT-MSCs after 28 days, the authors came to the conclusion that the benefit of AT-MSCs comes more from the release of soluble neurotrophins by the cells than from their incorporation or transdifferentiation into the host tissue.

The impact of MSCs and their secretome were investigated by Sun et al. [75] on ED induced by diabetes in rats. The study found that rats treated with ICIs of either MSCs or MSC secretome showed some improvement in erectile function in comparison with the untreated controls, as measured by intracavernous pressure to mean arterial pressure ratio, after 4 weeks. However, the impact was less pronounced in the MSC secretome group. The cavernosal tissue's nerve fibers showed an increase in nNOS and neurofilament immunostaining positivity along with the improvement. The therapeutic effects were likely due to MSCs-derived neurotrophins, such as

brain-derived neurotrophic factor and nerve growth factor, which were highly expressed in MSC secretome. Research in the field of neurology has confirmed that MSCs can enhance the recovery of the central nervous system in *in vivo* models of neurodegenerative diseases by releasing neurotrophins such as brain-derived neurotrophic factor, glial cell derived neurotrophic factor, and neurotrophin-3 [75,76]. The positive impact of MSC secretome on the central nervous system after pudendal nerve injury in a stress urinary incontinence model suggests that the improvement in erectile function following stem cell transplantation may also be attributed to the neuroregenerative properties of the MSC secretome [77].

Kim et al. [3] looked into the possibility of using human MSC secretome to treat ED. Using three-dimensional spheroid culture with MSCs obtained from bone marrow and cut-off filtering, they created a high concentration of MSC secretome. They next used biochemical assays to determine the composition of the secretome. A rat model of CNI was used in animal research to assess the therapeutic effects of MSC secretome. The findings showed that MSC secretome has therapeutic effects that are dose-dependent in mending damaged cavernosal tissue and regaining erectile function. These effects include angio- and neuro-trophic effects *in vivo*. The authors concluded that MSC secretome has significant potential for treating ED.

The potential of PSCs and their secretome as a therapy for ED caused by neurovascular injury was examined by Matz and colleagues [5]. The study found that PSCs secreted a significantly higher level of at least 27 growth factors and cytokines compared to other cell types. Additionally, either a single injection of PSC secretome or PSCs drastically enhanced erectile functional recovery and histological architecture in comparison to the control groups. The study suggests that the secretome isolated from human PSCs has the potential to be used as a effective injectable cell-free therapeutic for treating neurovascular injury-induced ED. Further research is needed to identify the unique protein expression within the PSC secretome to improve the treatment efficacy.

A research conducted by Zhang et al. [68] investigated the potential therapeutic efficiency of lipopolysaccharide-preconditioned allogeneic AT-MSCs (L-AT-MSCs) for treating ED caused by CNI in rats. The study found that low-dose lipopolysaccharide could enhance the survival of AT-MSCs, hinder the activation of caspase 3, and promote cell migration. Furthermore, L-AT-MSCs were found to be more effective in reducing fibrosis in the corpus cavernosum smooth muscle cells compared to AT-MSCs. L-AT-MSCs treatment increased erectile performance in rats 2 weeks following CNI, according to the *in vivo* investigation, by raising smooth muscle content and lowering penile fibrosis. These results were attributed to an increase in myelin basic protein and hepatocyte growth factor content in the corpus cavernosum and major pelvic ganglion, respectively. The results imply that L-AT-MSC therapy may be a hopeful strategy for regaining erectile function following CNI.

Recent research has suggested that the positive effects of MSCs on erectile function may be because of the therapeutic properties of their exosomes, which are small membrane-bound vesicles that contain various substances such as noncoding RNAs, proteins, and lipids [78]. These exosomes have been shown to play a fundamental function in intercellular communication and can have different effects depending on their source and activation status [79,80]. For instance, Lai et al. [81] disclosed that MSCs-derived exosomes had a protective effect on cardiac tissue after a heart attack. Zhang and colleagues [82] proved that exosomes produced by MSCs were helpful in the healing process of rats with traumatic brain injury. This was achieved by enhancing natural growth of blood vessels and nerve cells. Exosomes have several benefits over stem cell therapy, including better stability and simpler storage, no risk of tumorigenesis, and less chance of rejection by the immune system [83].

Table 2 summarizes the utilization of stem cells-derived exosomes for treatment of ED in animal models. Research has shown that exosomes derived from stem cells can increase the expression of certain biomarkers such as CD31, α-smooth muscle actin (α-SMA), eNOS, and nNOS in rats with ED. These markers are indicative of the contents of endothelium and smooth muscle in the corpus cavernosum. This suggests that exosomes may enhance the corpus cavernosum tissue structure, enhancing erectile function. Furthermore, the expressions of TGF-β1 and caspase 3 was decreased via the administration of exosomes derived from stem cells. TGF-β1 is known to participate in the development of corporal fibrosis, which is related to conditions such as Peyronie's disease [84]. Previous research has shown that TGF-β1 signaling can lead to collagen accumulation and deposition [85]. Exosomes have been shown to have antifibrotic effects in other diseases, such as lung and liver fibrosis. The decreased expression levels of TGF-β1 suggests that exosomes may also have an antifibrotic effect on ED [86].

An ischemia and hypoxic condition of the corpus cavernosum, which may enhance the generation of reactive oxygen species and cause cell death, was a hallmark of artery injury-induced ED [87]. A key element in the development of ED is oxidative stress in penile ischemia [87]. Stem cells-derived exosomes were discovered to reduce the expression of TGF-1 and caspase 3, indicating their capacity to prevent fibrosis and apoptosis and preserve the corpus cavernosum functional endothelium and smooth muscle contents. Downregulation of the NO/cyclic guanosine monophosphate (cGMP) signaling pathway, which is essential for controlling penile erection, causes ED [88]. NO, which is produced by eNOS in cavernous endothelium cells and nNOS in cavernous neurons, induces erection by raising the concentration of cGMP in the corpus cavernosum smooth muscle cells [89]. According to the work conducted by Song and colleagues [90], the application of exosomes from smooth muscle cells can improve ED by regulating the NO/cGMP pathway. The therapy was found to up-regulate the expression of nNOS and eNOS, suggesting that exosomes derived from stem cells may bring about functional improvements in the corpus cavernosum through this signaling pathway.

Most studies on exosomes for treating ED have focused on those derived from MSCs, which can be obtained from various tissue including adipose tissue, bone marrow, neonatal teeth, umbilical cord blood, and Wharton jelly tissue [54]. AT-MSCs and BM-MSCs are the most frequently exploited [54]. Stem cell-derived exosomes contain noncoding RNAs, such as transfer RNA (tRNA), small nucleolar RNA and microRNA (miRNA), which play important biological roles by inheriting characteristics of their parent cells.

Table 2 Utilization of stem cells-derived exosomes to treat erectile dysfunction in animal models.

Study	Producer cell	Isolation method	Exosome dose, μg	Cargo	ED model[a]	Establishment method	Injection method	Investigated parameter
Chen et al., 2017 [102]	AT-MSCs	Multistep centrifugation	100	miR-301a-3p	T2DM	High-fat diet, intraperitoneal injection of 30 mg/kg STZ	ICI	Bcl-2, caspase 3, ICP/MAP, and CD31
Liang et al., 2021 [103]	AT-MSCs	ExoQuick-TC (Systems Biosciences, Palo Alto, CA, USA)	400	NM	Hypoxia	Chronic intermittent hypoxia exposure	ICI	α-SMA, eNOS, and ICP/RT-AP
Song et al., 2020 [90]	AT-MSCs and BM-MSCs	Multistep centrifugation	100	NM	T1DM	Intraperitoneal injection of 60 mg/kg STZ	ICI	cGMP, ICP/MAP, and NO
Li et al., 2018 [104]	BM-MSCs and AT-MSCs	Ultracentrifugation and ultrafiltration	100	Corin	CNI	Bilateral cavernous nerve crush injury	ICI	α-SMA, ratio of smooth muscle to collagen content, nNOS, and vWF
Wang et al., 2020 [93]	AT-MSCs	Ultracentrifugation and ultrafiltration	200	NM	T1DM	Intraperitoneal injection of 60 mg/kg STZ	Intravenous	ICP/MAP, ANP, BNP, and nNOS
Liu et al., 2019 [105]	BM-MSCs	Multistep centrifugation	50 or 100	NM	AI	Internal iliac artery ligation	ICI	eNOS, α-SMA, ratio of smooth muscle to collagen content, ICP/MAP, CD31, VEGF, and nNOS
Ouyang et al., 2018 [83]	BM-MSCs	Multistep centrifugation	100	NM	CNI	Bilateral cavernous nerves crush injury	ICI	ICP/MAP, nNOS, ratio of smooth muscle to collagen content, and caspase 3
Liang et al., 2022 [106]	AT-MSCs	Differential centrifugation	150	NM	CNI	Bilateral cavernous nerves crush injury	ICI	α-SMA, eNOS, nNOS, and mICP/MAP
Zhu et al., 2018 [92]	AT-MSCs	Exosome precipitation solution and ExoQuick (System Bioscience, Mountain View, CA, USA)	10 or 100	miRNAs	T1DM	Intraperitoneal injection of 60 mg/kg STZ	Corpus cavernosum injection	Ratio of smooth muscle to collagen content, endothelial content, and ICP/MAP
Yang et al., 2020 [107]	HUSCs	Ultracentrifugation and ultrafiltration	100	NM	PD	Intratunical injection of TGF-β1	Intratunical	Collagen III, ratio of smooth muscle to collagen content,

(*continued on next page*)

Table 2 (*continued*)

Study	Producer cell	Isolation method	Exosome dose, μg	Cargo	ED model[a]	Establishment method	Injection method	Investigated parameter
								Smad2/3 protein, ICP/MAP, elastin, and TGF-β1
Ouyang et al., 2019 [108]	HUSCs	Ultracentrifugation	100	miRNAs	T1DM	Intraperitoneal injection of 60 mg/kg STZ	ICI	nNOS, ratio of smooth muscle to collagen content, CD31, eNOS, and phospho-eNOS

α-SMA, alpha-smooth muscle actin; AI, arterial insufficiency; ANP, atrial natriuretic peptide; MSCs, mesenchymal stem cells; AT-MSCs, adipose tissue-derived MSCs; Bcl-2, B-cell lymphoma 2; BM-MSCs, bone marrow-derived MSCs; BNP, brain natriuretic peptide; CD31, cluster of differentiation 31; cGMP, cyclic guanosine monophosphate; CNI, cavernous nerve injury; eNOS, endothelial nitric oxide synthase; HUSCs, human umbilical cord-derived stem cells; ICI, intracavernosal injection; ICP/MAP, intracavernosal pressure and mean arterial pressure; mICP/MAP, maximal ICP/MAP; miRNA, microRNA; NM, not mentioned; nNOS, neuronal nitric oxide synthase; vWF, von Willebrand factor; NO, nitric oxide; PD, Peyronie's disease; RT-AP, intracavernosal pressure/reactive hyperemia response to acetylcholine provocation; Smad2/3, mothers against decapentaplegic homolog 2/3; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TGF-β1, transforming growth factor beta 1; VEGF, vascular endothelial growth factor.

[a] Sprague–Dawley rats.

For instance, tRNAs make up over 50% of small RNAs in AT-MSCs-derived exosomes, while only 23%–25% are found in BM-MSC-derived exosomes. Interestingly, exosomes were found to contain higher levels of certain tRNAs compared to their source cells, indicating potential preferential sorting and release [91]. miRNAs were identified as the primary small RNA content in MSCs, and the presence of specific miRNAs with proangiogenic and antifibrotic functions (such as miR-let7b, miR-let7c, miR-132, miR-130a, and miR-126) was observed in AT-MSCs-derived exosomes by Zhu et al. [92]. Additionally, proteins present in the exosome membrane and vesicles are participated to both inter- and intra-cellular signaling mediation. In order to treat ED in diabetic rats, the transmembrane serine protease corin present in exosomes generated from AT-MSCs was exploited by Wang et al. [93] perhaps through triggering the atrial natriuretic peptide/NO/cGMP signaling cascade.

5. Hurdles in clinical translation

Although utilizing the secretome of stem cells shows a promising alternative to stem cell therapies, there are still several challenges that need to be addressed before it can be used clinically. One of the main hurdles in stem cell secretome research is devising a treatment plan that takes into consideration the intricate interplay of paracrine components following damage [94]. It will be easier to create more efficient protein-based conditioning techniques if we have a deeper comprehension of how cytokines are released during wound healing and injury, and how they affect the therapeutic benefits of stem cells. Further research is needed to identify the factors behind the therapeutic effects of secretome and to characterize it better. Furthermore, it should be noted that some molecules within the secretome, such as TNF-α or interleukin 6, may have negative effects [95]. To overcome this hurdle and make secretome a viable clinical option, there needs to be a better understanding of the molecular mechanisms that regulate the expression of secretome and its composition. This will enable better regulation of its production. Additionally, by understanding the effects of stem cell preconditioning or genetic manipulation approaches, it may be possible to modify the secretion profile of the secretome to enhance its therapeutic effects.

There are also some drawbacks to using conditioned media as an alternative to administering stem cell secretome. Firstly, the dynamic expression profile of stem cells cannot be accurately captured by the static composition of conditioned medium. Moreover, conditioned medium contains proteins released during cell death, which is not an accurate representation of the secretome. Therefore, careful optimization is required for each cell type to prevent the leakage of intracellular proteins from apoptotic cells [96]. Finally, producing and concentrating sufficient quantities of secreted molecules for clinical use is a challenging task.

There are many disadvantages to using conditioned media instead of stem cell secretome [76]. For instance, the fixed composition of conditioned media cannot accurately reflect the changing expression profile of stem cells, and proteins released during cell death may be present,

thereby not representing the true secretome. Additionally, it can be challenging to produce and concentrate sufficient quantities of secreted molecules for clinical use. Furthermore, protein stability, tissue transport, and pharmacokinetics must also be considered when administering secretome therapy. To achieve a regulated release of stem cell conditioned medium, it may be necessary to combine the distribution of these bioactive compounds with engineered biomaterials. Timing is also a crucial factor in clinical application, as different durations and time points of granulocyte-colony stimulating factor therapy following myocardial infarction have yielded varying patterns of effectiveness [97]. This emphasizes the requirement for a better comprehension of the secretome's function in stem cell recruitment and wound regeneration at various stages of injury. For therapeutic benefit, early delivery of stem cell-based therapies may be needed, which creates obstacles in patient identification, recruiting, and therapy administration. Moreover, the utilization of single cytokines for clinical purposes has been tested, but these trials have not been successful in meeting expectations due to concerns about safety, tolerability, and efficacy [98]. Similar difficulties may arise when using stem cell-conditioned medium, which contains a number of chemicals with various effects on host cells. The administration of angiogenic agents may also have long-term consequences, such as an increased risk of neoplasia or retinopathy [99]. Patients undergoing therapy must be thoroughly screened and followed up for these diseases, even though no link has been established in clinical studies between the administration of angiogenic cytokines and these pathologic processes.

6. Conclusion

Since the 1970s, when MSCs were first discovered in bone marrow, several more sources of MSCs have been found and are now being employed for various clinical illnesses, including cardiovascular, autoimmune, neurodegenerative, and urologic purposes. The ability of systemically delivered stem cells to target areas of acute injury, the capacity for multipotent differentiation, and the paracrine or autocrine action of stem cell secretome—which includes immunomodulatory and anti-inflammatory effects as well as the capacity to either start or assist in tissue regeneration—are three primary functions that are linked to stem cells' therapeutic potential. The significance of the stem cell secretome's paracrine or autocrine function is gaining more attention, and research has revealed that stem cell-specific factors play a crucial role in treating various diseases. However, the study of MSC secretome, particularly in relation to ED, is still in its early stages. The analysis of the numerous soluble components that make up the secretome has already been made easier by developments in high-throughput technologies, bioinformatics, and protein microarray. These developments will also continue to make it easier to identify the secretome contents of various stem cell types under various conditions. Currently, researchers are focusing on the autocrine and paracrine functions of the stem cell secretome, which has been found to be crucial in treating various diseases. However, there is still a lack of understanding about the MSC secretome and its role in treating ED. Advanced technologies such as protein microarrays and bioinformatics are being used to analyze the different soluble factors that make up the secretome and identify their contents under different conditions. While the secretome has been found to play a significant function in essential cellular processes, such as angiogenesis, revascularization, immune modulation, inflammation, wound healing, and tissue repair, there are still several obstacles that need to be overcome before it can be used as a practical choice for stem cell-based regenerative treatments. To better comprehend the intricate processes involved in stem cell—tissue interaction and translate these results into clinically useful outcomes, researchers need more reliable models, both *in vitro* and *in vivo*. Prior to clinical application, it is important to thoroughly address practical issues such as timing and method of drug administration following damage, regulation and dose of bioactive compounds, and safety. With the potential to resolve concerns regarding the application of stem cells and provide personalized, individualized therapy by alteration of secretome contents or delivery mode, the MSC secretome exhibits promise as an unique alternative to cell-based regenerative medicine therapies.

Author contributions

Study concept and design: Ria Margiana, Younes Pilehvar.
Data acquisition: Fatkhurrohmah L. Amalia, Silvia W. Lestari, Supardi Supardi.
Data analysis: Ria Margiana, Younes Pilehvar, Reny I'tishom.
Drafting of manuscript: Ria Margiana, Fatkhurrohmah L. Amalia, Reny I'tishom.
Critical revision of the manuscript: Ria Margiana, Younes Pilehvar, Reny I'tishom.

Conflicts of interest

The authors declare no conflict of interest.

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