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Exosomes derived from mesenchymal stem cells: Heralding a new treatment for periodontitis?

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ABSTRACT

Periodontitis, as a complex inflammatory disorder, is characterized by continuous destruction of the teeth-supporting components, like alveolar bone and periodontal ligament, and affects a great percentage of individuals over the world. Also, this oral disease is linked with multiple serious illnesses, e.g., cardiovascular disorders, diabetes, and oral cancer; thus, exerting efficient therapy for periodontitis is necessary. Unfortunately, the current therapies for the disease (e.g., surgical and nonsurgical methods) have not reflected enough effectiveness against periodontitis. At present, mesenchymal stem cell (MSC)-based remedy has created new hope for curating different diseases; however, MSCs have no capability to engraft into the chosen tissue, and the tumorigenic influences of MSCs are still the main concern. Interestingly, documents have revealed that MSC-derived mediators, like exosomes, which their exploitation is more feasible than intact MSCs, can be an effective therapeutic candidate for periodontitis. Therefore, in this study, we will review evidence in conjunction with their possible curative impacts on periodontitis cases.

1. Introduction

Almost 11% of subjects around the world suffer from a severe stage of periodontitis (Pan et al., 2019). Periodontitis, as a chronic complex inflammatory condition, is defined by the progressive demolition of the teeth-protecting components, such as alveolar bone and periodontal ligament, and is related to dental plaque accumulation, which is finally called dental biofilm (Kwon et al., 2021; Aref Nezhad et al., 2022). Multiple risk factors have been mentioned for the disease, including smoking, aging, psychological stress, and diabetes (Van Dyke and Dave, 2005). The key factor for periodontitis occurrence is bacterial invasion or toxins, but the pathogenesis of the disease is strongly influenced by host immune responses (Kim et al., 2021). This common oral disorder is also associated with several serious ailments, such as cardiovascular disorders, diabetes, oral cancer, Alzheimer's disease, rheumatoid arthritis, and metabolic syndrome (Corredor et al., 2022; De Araújo Silva et al., 2022; Dhingra, 2022; Kotin et al., 2022; Sansores-España et al., 2021; Payne et al., 2015). From a clinical viewpoint, periodontitis can be recognized based on its manifestations, like biofilm accumulation, bleeding, periodontal pocket formation, halitosis, clinical attachment loss (CAL), tooth mobility, and gingival recession (Abdulkareem et al., 2021; Chapple, 2009; Tonetti et al., 2018). However, proposed therapeutic ways for periodontitis, e.g., nonsurgical (scaling, root planning, and auxiliary antibiotics) and surgical remedies, have not reflected promising overlooks for patients due to their low effectiveness (Yang et al., 2021). Therefore, finding a potential treatment with high efficiency and low adverse impacts seems to be necessary (Pihlstrom et al., 2005). Recently, mesenchymal stem cells (MSCs) have created a bright horizon for treating various diseases, such as periodontitis (Novello et al., 2021). MSCs are known as adherent spindle-shaped cells with the capacity to differentiate into various cell types for the regeneration of damaged tissues (Rezaei-Tazangi et al., 2020). This type of

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stem cell can be obtained from diverse sources, like adipose tissue, bone marrow, umbilical cord, dental pulp, etc., and are capable of exerting immunoregulatory, anti-inflammatory, and paracrine influences (ArefNezhad et al., 2021; Bashiri et al., 2018; Hosseini et al., 2018; Rezaei-Tazangi et al., 2021; Rodini et al., 2018). Despite these, evidence expressed that MSCs are not facilely engrafted into the desired tissue, and the tumorigenic effects of MSCs are controversial yet (Rodini et al., 2018; Amiri et al., 2015). Fortunately, MSC-originated mediators, for instance, exosomes, can be used as an alternative approach for treating various disorders, and their use is more feasible than intact MSCs for repairing injured tissues (Zhou et al., 2018; Qiu et al., 2018; Yeo et al., 2013). Exosomes are released to the extracellular space by the fusion of plasma membrane with certain endosomes named multivesicular bodies (MVB) (Savina et al., 2003; Ebrahimi et al., 2022). Exosomes, which are in the range of 30–150 nm, are types of extracellular vesicles (EVs) important for cell-cell interrelationships in normal and abnormal situations and can transport functional proteins, nucleic acids, and other metabolites (Perocheau et al., 2021; Rezaie et al., 2022a,2022b,2022c). These EVs have specific properties, for instance, they possess a 1.08–1.19 g/ml density range and common exosome landmarks (e.g., CD9, Alix, Tsg101, CD63, CD82, and CD81). Moreover, they are stably present in the majority of body fluids and prevent the degradation of biomolecules (Rezaie et al., 2022a,2022b,2022c; Feghhi et al., 2021). In this line, some documents highlight the therapeutic influences of exosomes derived from MSCs in periodontitis treatment (Chew et al., 2019; Nakao et al., 2021). Hence, this review study aimed to summarize evidence regarding the probable therapeutic function of these MSC-originated agents against periodontitis.

2. Periodontitis and its pathogenic mechanisms

Periodontitis can result from the interplay of host, microbial, genetic, and environmental (age, diet, and smoking) factors (Yücel, 2015; Lod et al., 2014). Regarding host factors, the adaptive and innate immune systems play a pivotal role in reacting to many microorganisms related to periodontal biofilm (plaque) (Kajiya and Kurihara, 2021). The responses of the host immune system activated by colonized pathogens on subgingival biofilm may result in the excessive formation of reactive oxygen species (ROS), leading to damage to the periodontal ligament, alveolar bone, gingiva, and other teeth-protecting tissues (Sui et al., 2020). Some gram-negative bacteria, e.g., *P. gingivalis* and *A. actinomycetemcomitans*, are able to produce subgingival plaques and subsequently are involved in periodontitis progression (Gölz et al., 2014). Also, other pathogens, like *Treponema denticola*, *Prevotella*, *Tannerella forsythia*, and *Campylobacter species*, have a close relationship with the disease (Pérez-Chaparro et al., 2014). Some of these bacterial agents have a substantial role in periodontitis pathogenesis in light of their lipopolysaccharides (LPSs) present in their cells. LPS stimulation can activate Toll-like receptors (TLR), which in turn trigger nuclear factor κB (NF-κB), named a sequence-specific transcription factor effective in inflammatory reactions (Kagiya, 2016; Venugopal et al., 2018). Activation of this transcription factor leads to the secretion of pro-inflammatory factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)− 1, IL-6, and IL-8 (Venugopal et al., 2018; Ma et al., 2011). These agents can influence the function of osteoclasts, osteoblasts, and leukocytes, as well as the tissue remodeling process (Cazalis et al., 2009; Sorsa et al., 2006; Birkedal-Hansen, 1993). TNF-α, IL-1, and IL-6 have a key role in matrix metalloproteinase (MMP) induction and bone resorption in periodontitis (Singh et al., 2014; Graves and Cochran, 2003; Ishimi et al., 1990). IL-8, previously named neutrophil-activating peptide-1 (NAP-1), can also take part in breaking down the periodontal tissue by activating and recruiting neutrophils in the inflamed gingiva (Baggiolini et al., 1989; Bastos et al., 2009). Neutrophils, T and B lymphocytes, and antigen-presenting cells create a complicated network of interplays between them and components of the humoral system, like the complement system, to integrate inflammatory and immune reactions in the periodontium (Hajishengallis, 2014; Gaffen and Hajishengallis, 2008; Garlet, 2010; Silva et al., 2015; Taubman et al., 2005; Berglundh et al., 2007). It is stated that the complement system, a strong effector associated with the innate and adaptive immune system, has synergistic effects with the action of TLR on leukocytes in addition to tagging and abolishing microbes and can modulate activating and differentiating the subsets of T cells and B cells (Dunkelberger and Song, 2010; Ricklin et al., 2010; Hajishengallis et al., 2017). In the mentioned disease, these complex interplays give rise to inflammation-stimulated bone loss. This process is mainly triggered by the receptor activator of nuclear factor-κB ligand (RANKL), its decoy receptor osteoprotegerin, and its functional receptor RANK (Fig. 1) (Tsukasaki et al., 2018; Hajishengallis et al., 2020). In the inflamed periodontium, RANKL, a subclass of the TNF gene family, is formed by osteoblasts and activated B and T lymphocytes (Tsukasaki et al., 2018; Roodman, 2006). From a genetic viewpoint, polymorphisms in the *TLR4*, *VDR*, *FcγRIIIb*, *IL1RN*, *IL6*, *CD14*, *IL10*, *MMP*, and *IL1B* genes may also be related to susceptibility to periodontitis (Laine et al., 2012).

3. Exosomes derived from mesenchymal stem cells and inflammation regulation

Inflammation is described as one of the leading processes for the initiation and development of various disorders, like periodontitis, cardiovascular disease, cancer, obesity, diabetes, inflammatory bowel disease, and osteoporosis (Glowacki et al., 2013; Laveti et al., 2013). This process is a key host defense reaction to injured tissues, infectious agents, and auto-immune responses (Laveti et al., 2013). The activity of inflammation can be categorized as acute or chronic (Luo et al., 2022). Acute inflammation is defined as an intense infiltration of neutrophils (polymorphonuclear leukocytes) and activation of macrophages differentiated from monocytes (Schwenck et al., 2020). Chronic inflammation is considered by injured tissue infiltration by mononuclear agents, like lymphocytes, plasma cells, and macrophages (Rajendran et al., 2018). Based on the present evidence, exosomes originating from MSCs have reflected a good potential for inflammation regulation. MSC-originated extracellular vesicles, such as exosomes, can significantly change the phenotypes of macrophages from M1 to M2 (Hu et al., 2019). M2 macrophages have the capability to secret factors effective in inflammation reduction and tissue reconstruction (Dauletova et al., 2021). MSC-derived exosomes are able to modulate B lymphocyte activation, differentiation, and proliferation and inhibit T-lymphocyte proliferation (Hu et al., 2019). B and T lymphocytes can be involved in inflammatory occurrences through the secretion of pro-inflammatory cytokines (Moro-García et al., 2018; Pala et al., 2018). Also, these exosomes convert T cells into T-regulatory cells (Hu et al., 2019). Other documents expressed that exosomes originated diverse types of MSCs are capable of diminishing the inflammatory occurrences triggered by different stimuli by down-regulating pro-inflammatory agents, for example, cyclooxygenase (COX)− 2, inducible nitric oxide synthase (iNOS), and chemokines and cytokines, such as monocyte chemoattract-ant protein (MCP)− 1, interleukin (IL)− 1β, and tumor necrosis factor (TNF)-α. Furthermore, MSCs-derived exosomes can up-regulate some anti-inflammatory cytokines, for instance, IL-10 (Yang et al., 2015; Li et al., 2016; Yu et al., 2016). In summing up, it seems that exosomes derived from MSCs can have a suitable capacity to regulate inflammation processes, likely through the enhancement of M2 macrophage polarization into M1 macrophages, promoting anti-inflammatory (e.g., IL-10) and attenuating pro-inflammatory agents (e.g., COX-2, iNOS, MCP-1, etc.).

4. Exosomes derived from mesenchymal stem cells and periodontitis

According to published scientific documents, exosomes derived from MSCs have positive effects on teeth-protecting components (Chew et al.,

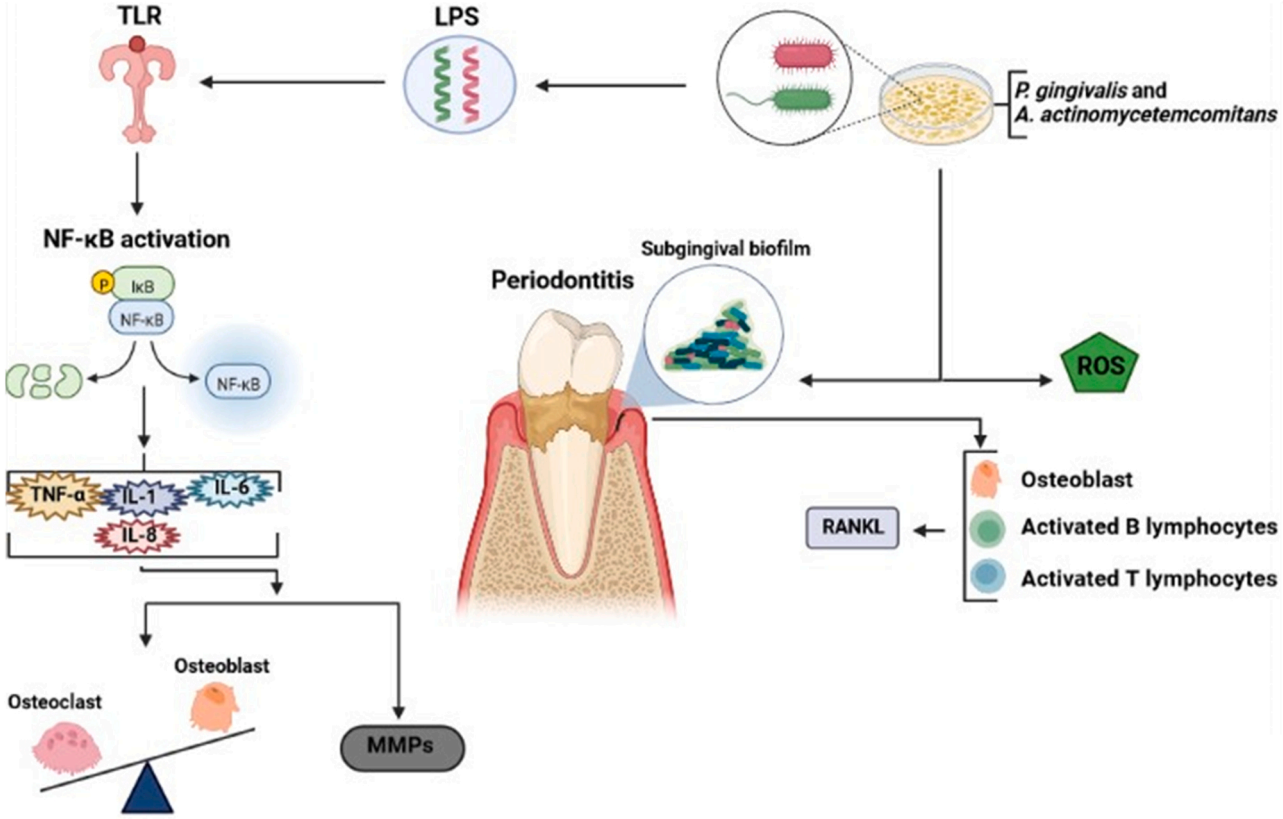

Fig. 1. Some pathogenic agents are involved in the onset and progression of periodontitis, especially immune and bacterial agents.

2019). In this line, in vivo and in vitro research demonstrated that this type of exosomes can potentiate periodontal tissue and bone regeneration and the proliferation and migration of periodontal ligament cells by triggering AKT and ERK signaling pathways by the mediation of adenosine receptors (Chew et al., 2019). Also, in an endeavor by Nakao et al., the therapeutic potential of human gingival MSC-derived exosomes preconditioned by TNF-α, an enhancer of MSC-derived exosome secretion, was investigated in a periodontitis mice model induced by a ligature (Nakao et al., 2021; Cheng et al., 2018). The reasons for selecting gingival tissue as a source of MSC-derived exosomes in this work were their easy isolation, rapid cell proliferation, and the capacity to release a great number of exosomes (Chew et al., 2019). Finally, their findings showed that the exosomes could diminish periodontal bone resorption, suppress osteoclast function, and enhance M2 macrophage polarization (Chew et al., 2019). Activated M2 macrophages are stimulated by some cytokines, like IL-4 and IL-13, and exert their anti-inflammatory impacts through the production of anti-inflammatory agents, such as VEGF, TGF-β, and IL-10 (Gordon and Martinez, 2010). Also, it has been implicated that human gingival MSC-derived exosomes decrease inflammatory reactions in periodontal ligament stem cells triggered by LPS by inhibiting the NF-κB and Wnt5a signaling pathways (Table 1) (Sun et al., 2022). Some reports also stated that dental pulp MSC-derived exosomes expedite the improvement of alveolar bone through some mechanisms, like the transfer of miR-1246 to immune agents and suppression of osteoclast formation (Shen et al., 2020; Shimizu et al., 2022a, 2022b). However, the yield of these exosomes is low, which is related to the isolation technique, culture system, and purification process (Zhang et al., 2020; Phan et al., 2018). It has been recommended that using a three-dimensional (3D) culture system can provide more exosomes and elevate the therapeutic impacts of the exosomes by transferring certain cargoes (Phan et al., 2018; Haraszti et al., 2018; Yan and Wu, 2020). In this direction, Zhang and colleagues utilized 3D-cultured dental pulp MSC-derived exosome and observed that these extracellular vesicles serve as an anti-inflammation agent in an animal model of periodontitis by recovering the Th17 cell/Treg balance (Zhang et al., 2021). Other sources of MSC-derived exosomes have similar effects on bone resorption or formation. For instance, exosomes originating from adipose tissue MSCs are able to decrease osteocyte apoptosis through the upregulation of the Bcl-2/Bax ratio and reduction of the formation of cytochrome c and ROS (Fig. 2) (Ren et al., 2019). Moreover, in the scientific project of Mohammed and co-workers, the effectiveness of exosomes originating from adipose tissue MSC against periodontitis was scrutinized (Mohammed et al., 2018). Adipose tissue MSCs can also be another good choice for exosome obtaining because they can be collected in large amounts with noninvasive methods with no ethical problems. In addition, they have immunoregulatory and anti-microbial influences and have the capability to differentiate into diverse cell types (Kocan et al., 2017). Mohammed et al., using the exosomes of this source, addressed the positive effects of the exosomes on the periodontitis rat model through the diminution of infiltration of inflammatory agents, increase in collagen synthesis, periodontal fibroblast proliferation, and osteoid tissue formation (Mohammed et al., 2018). A recent study also highlighted the beneficial influences of exosomes obtained from human bone marrow stromal cells, one of the safe sources rich in growth factors and cytokines useful in regenerative medicine, on periodontitis in vivo and in vitro (Yue et al., 2022; Scheiber et al., 2022; Saito et al., 2012). They observed that these nano-sized agents curb inflammatory reactions caused by *P. gingivalis*, a periodontal keystone pathogen. Plus, a decrease in gingival tissue destruction and infiltration of immune cells were other findings (Yue et al., 2022). Evidence indicates that MSC-derived exosomes can be an effective therapeutic tool against periodontitis; however, more scientific efforts are demanded to approve their efficacy on the disease.

Table 1
Exosomes originated from different sources of mesenchymal stem cells by various mechanisms can be helpful in periodontitis treatment.

Type of MSC-derived exosome	Effect/ mechanisms	*In vivo*/ in vitro	References
Collagen sponge loaded with human MSC-derived exosome	Increasing proliferation and migration of periodontal ligament cells and infiltration of fibroblast-like cells	*In vivo* and in vitro	(Chew et al., 2019)
Human gingival MSC-derived exosome preconditioned by TNF-α	Reducing periodontal bone resorption, increasing M2 macrophage polarization, and exerting anti-osteoclastogenic effects	*In vivo*	(Nakao et al., 2021)
Human gingival MSC-derived exosome	Reducing inflammatory reactions	*In vitro*	(Sun et al., 2022)
Periodontal ligament stem cell-derived exosome	Elevating the expression of osteogenic protein and genes, production of mineralized nodules, and improving bone regeneration	*In vivo* and in vitro	(Lei et al., 2022)
Human dental pulp MSC-derived exosome	Enhancing the migration of human dental palp and osteoblastic cells, and inhibiting alveolar bone resorption and osteoclast formation	*In vivo* and in vitro	(Shimizu et al., 2022a,2022b)
3D-cultured dental pulp MSC-derived exosome	Recovering the Th17 cell/ Treg balance	*In vivo*	(Zhang et al., 2021)
Adipose tissue MSC-derived exosome	Reducing inflammatory infiltration, increasing the proliferation of periodontal fibroblasts and formation of osteoid tissue	*In vivo*	(Mohammed et al., 2018)
Human bone marrow stromal cell-derived exosome	Inhibiting inflammatory responses and reducing the infiltration of immune cells	*In vivo* and in vitro	(Yue et al., 2022)

5. Potential and challenges related to the application of mesenchymal stem cells-derived exosomes in the clinic

EVs, like exosomes, in light of multiple advantages related to their structures, i.e., suitable biocompatibility, low immunogenicity, nano-size scale, engineering facility, and the ability for loading different cargos, can create a potent therapeutic chance for clinical applications (Rezaie et al., 2022a,2022b,2022c; Ahmadi et al., 2022). Also, the utilization of these EVs rather than MSCs can decrease cell therapy-related complications, like infusional toxicities (Mendt et al., 2019). Recently, several clinical trials have been registered regarding the effects of MSC-derived EVs on different problems, like periodontitis, acute myocardial infarction, coronavirus disease 2019 (COVID-19), Crohn's Disease, burn wounds, and ulcerative colitis (Kou et al., 2022). Also, some published clinical trials reflected the beneficial effects of MSC-derived EVs on various illnesses. For example, in a single-center randomized clinical trial, it was shown that the administration of umbilical cord MSC-derived EVs can remarkably improve estimated glomerular filtration rate (eGFR), blood urea, urinary albumin creatinine ratio (UACR), serum creatinine level, IL-10, and TGF-β1 plasma levels and reduce TNF-α plasma level in patients with chronic kidney disease (Nassar et al., 2016). Dehghani et al. (2022) in a randomized clinical trial, concluded that intraparenchymal injection of exosomes derived from placenta MSC has no detrimental impacts on subjects with ischemic stroke and can be exploited as a reparative and preventive therapeutic tool in cases suffering from this disorder (Dehghani et al., 2022). Interestingly, the results of the evaluation of the effects of MSC-derived EVs on COVID-19 subjects have been published recently. For instance, Sengupta et al. revealed that the administration of a single dose of exosomes originating from bone marrow MSCs leads to hypoxia improvement and cytokine storm reduction in hospitalized cases with severe COVID-19 (Sengupta et al., 2020). In another scientific effort, it was approved that the nebulization of umbilical cord MSC-derived exosomes does not trigger allergic reactions but potentiates pulmonary lesion absorption and decreases hospitalization duration for COVID-19 pneumonia patients in the mild stage (Zhu et al., 2022). There are also challenges concerning the utilization of EVs in the clinic: (A) EVs are heterogeneous in terms of activity, content, and size. (B) The amount of EVs is not generally high at desired tissue because they are trapped by the lungs, spleen, and liver organs following their intravenous admiration. (C) The methods for preparing MSCs-EVs require more support and optimizing instructions because scientists used various approaches for the delivery of MSCs-EVs. (D) To acquire a suitable concentration of EVs, a large amount of MSCs is necessary. (E) Modification techniques, particularly genetic engineering on the membrane and content of EVs, may change the function and morphology of EVs, leading to detrimental influences on desired cells/tissues (Rezaie et al., 2022a,2022b,2022c; Rezaie et al., 2022a,2022b,2022c). Despite the promising results documented by a large number of scientists, the majority of investigations were accomplished in preclinical situations, and there is a main need for clinical studies to illustrate the effectiveness of MSCs-EVs in the clinic.

6. Conclusion

Periodontitis is an oral inflammatory illness that involves a considerable population of people globally and influences the life quality of patients negatively. Unfortunately, the current treatments for the disease, like surgical and nonsurgical methods, have not met the expectations of patients yet, and there is a need for exploring an effective alternative method for these cases. These days, MSCs have acquired specific attention in the therapy of various disorders; however, they are not easily engrafted into the selected tissue, and their tumorigenic potential is controversial yet. Newly, using exosomes derived from different sources of MSCs, like gingival, dental pulp, adipose tissue, and bone marrow, has been suggested as an alternative method for periodontitis. It seems that they can be effective in diseases treatment by diverse mechanisms, such as decreasing periodontal bone resorption, inflammatory reaction, osteocyte apoptosis, and ROS formation, elevating collagen synthesis, periodontal fibroblast proliferation, and osteoid tissue formation, inhibiting osteoclast function, and enhancing M2 macrophage polarization; However, more in vivo and in vitro investigations are needed to declare that they can be helpful surly in the fight with the disease.

Ethical approval

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CRediT authorship contribution statement

Elnaz Mousavi, Armin Khosravi and Somaye salari sedigh contributed to the acquisition, analysis, and interpretation of data for the work. Sayad ayub tabatabaei mayanei, Morteza Banakar, Moslem Karimzadeh and Amirhossein Fathi contributed to the write-up of the review article.

Conflict of interest

The authors declare no conflict of interest.

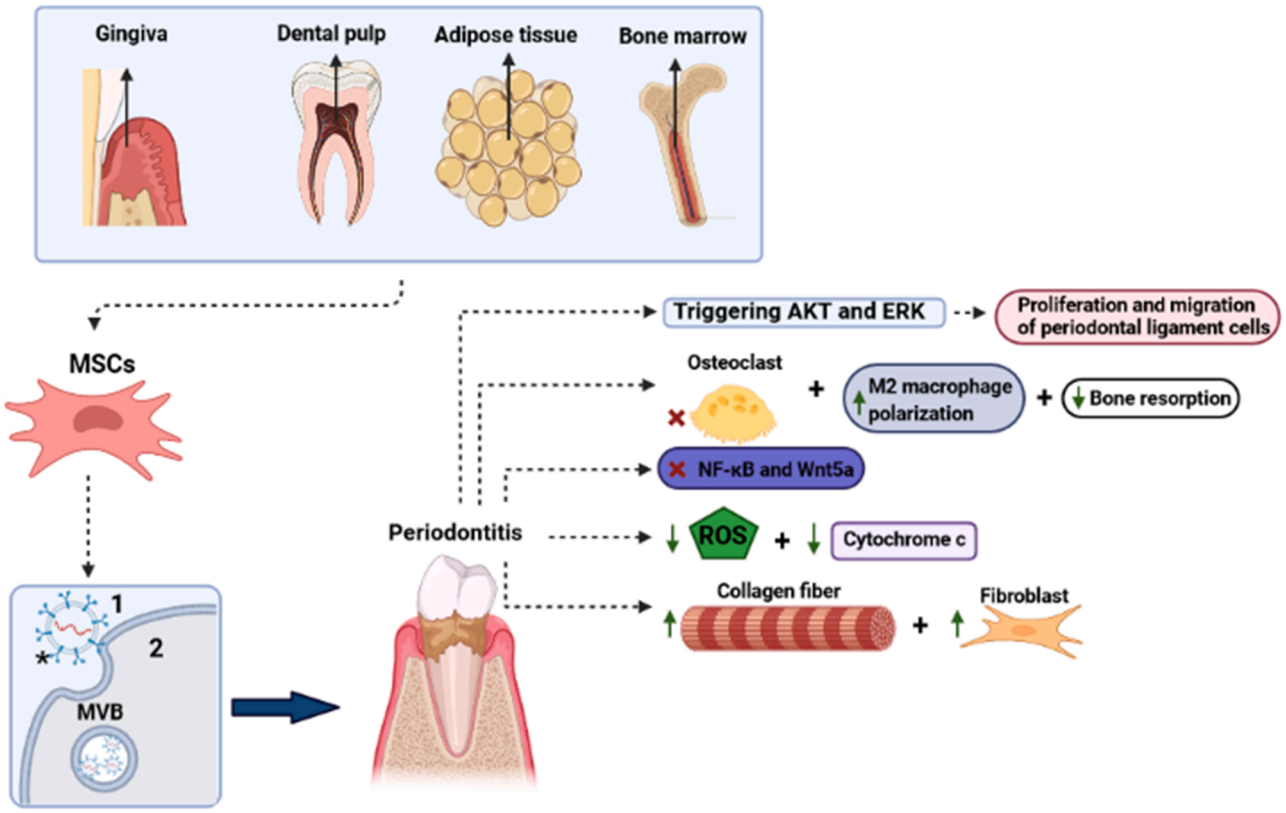

Fig. 2. Exosomes derived from gingival, dental pulp, adipose tissue, and bone marrow mesenchymal stem cells can target periodontitis. 1, Extracellular space; 2, intracellular space; *, Exosome.

Data Availability

Data will be made available on request.

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