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Angiogenic Potential of Various Oral Cavity–Derived Mesenchymal Stem Cells and Cell-Derived Secretome: A Systematic Review and Meta-Analysis

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Abstract

Recent evidence suggests the immense potential of human mesenchymal stem cell (hMSC) secretome conditioned medium-mediated augmentation of angiogenesis. However, angiogenesis potential varies from source and origin. The hMSCs derived from the oral cavity share an exceptional quality due to their origin from a hypoxic environment. Our systematic review aimed to compare the mesenchymal stem cells (MSCs) derived from various oral cavity sources and cell-derived secretomes, and evaluate their angiogenic potential. A literature search was conducted using PubMed and Scopus from January 2000 to September 2020. Source-wise outcomes were systematically analyzed using *in vitro*, *in vivo*, and *in ovo* studies, emphasizing endothelial cell migration, tube formation, and blood vessel formation. Ninety-four studies were included in the systematic review, out of which 4 studies were subsequently included in the meta-analysis. Prominent growth factors and other bioactive components implicated in improving angiogenesis were included in the respective studies. The findings suggest that oral tissues are a rich source of hMSCs. The meta-analysis revealed a positive correlation between dental pulp–derived MSCs (DPMSCs) and stem cells derived from apical papilla (SCAP) compared to human umbilical cord–derived endothelial cell lines as a control. It shows a statistically significant positive correlation between the co-culture of human umbilical vein endothelial cells (HUVECs) and DPMSCs with tubule length formation and total branching points. Our

Keywords
- secretome
- angiogenesis
- angiogenic growth factors
- cytokine analysis

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meta-analysis revealed that oral-derived MSCs (dental pulp stem cells and SCAP) carry a better angiogenic potential *in vitro* than endothelial cell lines alone. The reviewed literature illustrates that oral cavity–derived MSCs (OC-MSCs) increased angiogenesis. The present literature reveals a dearth of investigations involving sources other than dental pulp. Even though OC-MSCs have revealed more significant potential than other MSCs, more comprehensive, target-oriented interinstitutional prospective studies are warranted to determine whether oral cavity–derived stem cells are the most excellent sources of significant angiogenic potential.

Introduction

Oral cavity–derived dental pulp stem cells (DPSCs) have gained attention due to their potential use in regenerative medicine. These stem cells are known for their unique characteristics that make them distinct from other stem cell sources. Some exceptional criteria of oral cavity–derived DPSCs are their mesenchymal stem cell (MSC) characteristics, ease of accessibility, multilineage differentiation, regenerative capacity with high angiogenic potential, and immunomodulatory properties with low immunogenicity. Despite their potential advantages, using oral cavity–derived stem cells for oral cancer treatment and reconstruction poses several challenges. Oral cancer creates a hostile tumor microenvironment characterized by inflammation, hypoxia, and immune suppression. Stem cells may face difficulty surviving and exerting their regenerative properties in such an environment. There is a risk that the harvested stem cell population could be contaminated with cancer cells, which can lead to cancer recurrence if transplanted back into the patient. Moreover, oral carcinoma contains a population of neoplastic cells with aggressive stem cells that are difficult to distinguish from healthy cells. Angiogenesis or neovascularization is a dynamic process involving new blood vessels that form from existing blood vessels.[1] Oral cavity stem cells secrete various angiogenic factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and others. These factors attract endothelial cells and support the formation of new capillaries.

Oral cavity stem cells can trigger angiogenesis when introduced into a tissue requiring regeneration or healing. It is crucial during development, along with various physiological and pathological processes.[2] Angiogenesis occurs lifelong, starting in the uterus and continuing into old age. Furthermore, capillaries are required to exchange nutrients and metabolites in all tissues.[3] Angiogenesis is paramount concerning wound healing due to its critical role in growing a new capillary network from the granulation tissue, which plays a pivotal role in chronic inflammation.[3] Wound healing is a complex procedure involving overlapping events, including inflammatory, proliferative, and remodeling phases. Many growth factors and cytokines participate in the proliferative phase, of which angiogenic growth factors hold a prime role.[4] Revascularization is regulated by a complex interaction between various growth factors, including but not limited to VEGF, FGF, angiopoietins (ANG), PDGF, transforming growth factor-α (TGF-α), and transforming growth factor-β (TGF-β).[5] Each factor plays a separate role in inducing, initiating, and amplifying cell proliferation, cell migration, stabilization, wound healing, inflammation, and suppression of angiogenesis.[1,6] Several growth factors like VEGF, FGF-2, and PDGF have been used clinically to augment angiogenesis for various therapeutic applications. However, lack of spatiotemporal control over the release of these proangiogenic proteins has led to numerous complications, including leaky vasculature. Cell-based therapies are evolving therapeutic options for deranged angiogenesis.[7]

MSCs derived from human placental tissue, bone marrow, or umbilical cord tissues provide a novel strategy for the induction of angiogenesis. Various studies have demonstrated the ability of MSCs to differentiate into endothelial cells and provide vascular stability. In addition, MSCs secrete an extended milieu of growth factors, cytokines, extracellular vesicles (EVs), and messenger ribonucleic acids (mRNAs) implicated in a wide range of biological processes. Interestingly, "secret factors" (secretomes) from MSCs promote angiogenesis and amend wound healing in virtue of potent paracrine signaling, yielding proangiogenic factors.[5] Although hMSCs isolated from various sources have exhibited proangiogenic potential, knowledge about the ideal source (cells or secretomes, source-wise potential, and ease of sample collection) remains obscure. Oral tissues originate from mesenchymal and ectodermal germ layers that add to their value, making them the ideal source for isolation and therapeutic applications. Stem cells are influenced by their *in vivo* environment, which projects through their therapeutic properties.[8] The stem cell niche includes cellular and extracellular matrix components, tissue location, innervation, and blood supply. The oral cavity is highly vascularized and yields better-quality stem cells with potent angiogenic potential. Rapid wound healing in the oral cavity can explain its unique potential. Their high proliferation and unique secretory profile can be attributed to their hypoxic condition. Oral cavity–derived cells are multipotent; primitive oral tissues such as dental follicles harbor oral cavity–derived MSCs (OC-MSCs). Therefore, MSCs isolated from various sources from the

oral cavity comprise a powerful weapon to battle numerous diseases.[9]

In recent decades, stem cell proliferation from various adult tissues has been a provoking tool in advanced sciences. Previous studies have revealed the role of dental pulp–derived MSCs (DPMSCs) and stem cells from human exfoliated deciduous teeth (SHED) in enhancing the cascade of angiogenesis. Our systematic review aimed to compare OC-MSCs and cell-derived secretomes and evaluate their angiogenic potential. The subsequent meta-analysis with compatible data analyses whether OC-MSCs (DPSC and stem cells derived from apical papilla [SCAP]) carry a better angiogenic potential *in vitro* than endothelial cell lines alone. Extensive collaborative research is required to conclude which oral-derived stem cells have the best angiogenic potential. This systematic review focuses on the potential of MSCs and their secretomes derived from various oral tissues such as gingival tissue, dental pulp, periodontal ligament (PDL), mandibular bone, and buccal fat, with particular emphasis on angiogenesis.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research proposal has been registered in PROSPERO (registration no: CRD42021282497).

Based on the PRISMA criteria, the research question for this review was framed in the PICO format as the following: Which is the best oral source of MSCs for augmenting angiogenesis at the implanted site?

The terms used to identify studies based on the elements of the PICO format were as follows:

- Population: i*n vitro* studies, *in vivo* studies, and ex vivo studies.
- Intervention: OC-MSCs.
- Comparison: between various OC-MSCs.
- Outcome: angiogenesis at the desired site of implantation.

The inclusion criteria of the study were the following:

- Articles published in the English language.
- Studies relevant to the topic published from January 1, 2000 to March 2023.
- Studies showing *in vitro*, *in vivo*, and *in ovo* results for angiogenesis of OC-MSCs.
- Studies having well-defined information regarding the angiogenic potential of OC-MSCs.

The exclusion criteria of the review included the following:

- Abstracts.
- Reviews.
- Letter to the editor.
- Editorials.
- Case reports.
- Short communication.
- Commentaries.
- Articles in languages other than English.

Systematic computer searches were performed on two electronic databases: PubMed and Scopus. The following keyword combinations were used to search articles:

- "Dental stem cells AND Angiogenesis AND conditioned media."
- "Dental stem cells AND Angiogenic potential AND conditioned media."
- "Dental stem cells AND Angiogenesis."
- "Dental stem cells AND Angiogenic potential."

Along with the electronic search, a hand search was also performed to find the missed articles. Articles published between January 1, 2000 and March 1, 2023 were included in the survey. Two reviewers (M.S. and S.K.) independently evaluated the titles and abstracts of the retrieved publications pertaining to the covered research topic during the initial screening. If material relevant to the inclusion criteria was provided in the abstract, or if the title was relevant but the abstract was unavailable, a full-text report was acquired. The complete text of the articles was then screened to find those that matched the inclusion criteria. If the work appeared to meet the inclusion criteria, the authors were contacted to seek further information. Articles with full-text reports only were evaluated in this systematic review. Studies that only published abstracts were removed because evidence revealed differences between data given in abstracts and those supplied in the final published complete report. Two review authors (M.S. and S.K.) separately collected data using a specifically designed data extraction sheet (►**Table 1**). A third (S.D.) and a fourth (Y.M.) reviewer handled any disagreements about the inclusion of publications or data extraction.

The following data items were extracted: authors and year of publication; source of stem cells used; type of study; model used for evaluating angiogenesis; growth factors assessed for angiogenesis; method used for analysis of angiogenesis; use of stem cells/conditioned media; use of preconditioning; use of co-culture with MSCs; and results obtained.

To evaluate an article's quality, we used the Joanna Briggs Institute appraisal checklist for a case-control study. Based on 10 prespecified questions in the tool, two researchers independently examined all case reports. Each question received one of the following statuses based on judgment: "yes," "no," "maybe," or "unclear." A quality grade was assigned to the listed studies, with scores over 70% deemed excellent. Scores between 40 and 70% were considered to be of moderate quality, while those under 40% were considered to be of low quality. The reviewers agreed on these criteria in order to provide a thorough and objective assessment of the research quality. Egger's regression test was used to identify publication bias in the selected articles for quantitative analysis.

Results

In an initial literature search, 1,025 articles (591 from PubMed and 434 from Scopus) were retrieved. The selection

Table 1 Tabular representation of qualitative data obtained from literature search for included studies

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
Dental pulp–derived mesenchymal stem cells (DPMSCs)										
1.	Li et al[10]	Dental pulp	*In vivo*	Mice	VEGFR1, VEGFR2, VE-cadherin, ETV2, and CD31	Real-time polymerase chain reaction (RT-PCR)	Cells	ETV2 transfected	Human umbilical vein endothelial cell (HUVEC)	Dental pulp stem cell (DPSCs) proved as potential candidates for clinical applications in therapeutic tissue engineering
2.	Boreak et al[11]	Dental pulp	In ovo	Yolk sac membrane (YSM)	VEGFA, FGF-2, CXCL8, VEGF, and angiopoietin-2	Enzymelinked immunosorbent assay (ELISA) and RT-PCR	Conditioned media	Metformin, cisplatin (negative control) L-arginine (positive control)	No	Metformin treated conditioned media derived from DPSCs enhanced the level of angiogenic activity in the YSM
3.	Li et al[12]	Dental pulp	*In vivo*	Rats	Angiogenin, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), HIF-1α, interleukin-8 (IL-8), monocyte chemotactic protein 1 (MCP-1), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF)	RT-PCR	Cells	No	No	Stem cells from the dental pulp provided greater therapeutic effects compared to stem cells from the umbilical cord
4.	Li et al[13]	Dental pulp	*In vivo*	Rats	VEGF, VEGFR-2 (Flk1)	RT-PCR and ELISA	Cells	Nell-1	HUVEC	Nell-1 could promote endothelial vessel formation and enhance the angiogenic factor expression when treated over the DPSCs or HUVECs
5.			*In vivo*	Mice	VEGF-A, FGF-2	RT-PCR	Cells		No	

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
	Alghutaimel et al[14]	Dental pulp						Decellularized dental pulp (DDP) matrix of bovine origin treated the DPSCs		DDP seeded along with the DPSCs provided greater angiogenic efficiency that singularly seeded the DDP
6.	Zhou et al[15]	Dental pulp	*In vitro*	HUVECs	VEGF	RT-PCR	Cells	Transfection of miR-378a. hedgehog/Gli1 signaling inhibition	HUVECs	Extracellular vesicles derived from the DPSC transfected with miR-378a could enhance angiogenic proliferation *in vitro*
7.	Huang et al[16]	Dental pulp	*In vitro*	HUVECs	VEGF and kinase-insert domain-containing receptor (KDR)	RT-PCR	Cells	Lipopolysaccharide (LPS)	HUVECs	Inflammatory stimulation
8.	Afami et al[17]	Dental pulp	*In vitro*	Microbes	Angiogenin, EGF, FGF, PDGF, INF-gamma, VEGF, insulinlike growth factor (IGF), and angiopoietin	Heat map	Both	(Naphthalene-2-ly)-acetyl-diphenylalanine-dilysine-OH (NapFFε-KεK-OH)	Hydrogel	Increased vascular components
9.	Liao et al[18]	Dental pulp	*In vivo*	Mice	VEGF and AngII	qRT-PCR analysis and immunofluorescence staining	Cells	No	No	Enhanced wound healing
10.	He et al[19]	Dental pulp	*In vitro*	C. albicans biofilms	Hyphal wall protein1 (hwp1), agglutininlike sequence protein 3 (als3) and cell surface hydrophobicity (csh1)	RT-PCR	Cells	Norspermidine (NSPD)	GelMA hydrogels	NSPD did not directly influence the angiogenic properties of the DPSCs
11.	Guo et al[20]	Dental pulp	*In vivo*	Rat	Angiogenin, EGF, bFGF, and HGF	Not mentioned	Cells	No	Human adipose microvascular	Co-culture of the DPSC with the HAMECs yielded

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
									endothelial cells (HAMECs)	denser vascular bundles compared to endothelial cells alone
12.	Luzuriaga et al[21]	Dental pulp	*In vitro*	Mouse liver sinusoidal endothelial cells (mLSECs)	VEGF	Flow cytometry	Cells	No	No	Use of the DPSC-enhanced prevascularized engraftments improves cell–graft integration compared to nonvascularized grafts
13.	Merckx et al[22]	Dental pulp	In ovo	Chorioallantoic membrane (CAM) of chicken embryos	Angiogenin, angiopoietin-1 (Angpt-1), HGF, insulinlike growth factor-binding proteins (IGFBPs), monocyte chemoattractant protein-1 (MCP-1), urokinase plasminogen activator (uPA), and VEGF	Transmission electron microscopy, high-resolution flow cytometry, and ELISA	Both	No	Co-culture with bone marrow–derived MSCs (BM-MSCs)	Positive paracrine effects on endothelial cell migration and *in ovo* blood vessel formation, with a stronger potential for BM-MSCs was found
14.	Caseiro et al[23]	Dental pulp	*In vivo*	Rats	Angiopoietin-2 (Ang), EGF, endothelin-1 (EDN1), fibroblast growth factor 1 and 2 (FGF-1 and FGF-2), PDGF-AA and PDGF-AB/BB, transforming growth factor alpha (TGFα), transforming growth factor	PCR	Both	No	Co-culturing was done with umbilical cord–derived MSCs	UC-MSCs provide a wider variety and greater concentration of relevant growth factors and cytokines

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
					beta 1, 2, and 3 (TGF-β1, -2, and -3), tumor necrosis factor alpha (TNFα), TNFβ, VEGF-A, VEGF-C, and VEGF-D					
15.	Makino et al[24]	Dental pulp	*In vivo*	Rats	TNF-α, VEGF, and bFGF	Immunohistological staining	Both	No	No	Increased capillary formation achieved
16.	Chen et al[25]	Dental pulp	*In vitro*	Endothelial cell line	VEGF, PDGF, SDF-1, and GAPDH	IHC and PCR	Cells	No	No	VEGF expression was higher in pulp tissue from teeth with deep caries (cDPMSCs) than in normal tissue
17.	Li et al[26]	Dental pulp	*In vitro*	Endothelial cell line	KDR and CD31	Immunofluorescence analysis and RT-PCR	Cells	No	Human decellularized dental pulp matrix (hDDPM)	Increased proliferation of blood vessel-like structures was evident
18.	Wang et al[27]	Dental pulp	*In vitro*	Endothelial cell line	VEGF	ELISA, two-photon laser microscopy	Cells	No	HUVECs	Extracellular vesicles from the DPMSCs can promote angiogenesis in an injectable hydrogel *in vitro*
19.	Zhou and Sun[28]	Dental pulp	*In vitro*	Endothelial cell line under hypoxic conditions	VEGF, FGF, vWF, VEGFR2, VE-cad, HIF-1α, and CD31	PCR	Cells	No	No	Hypoxic conditions enhanced the tube formation of the DPMSCs *in vitro*
20.	Qu et al[29]	Dental pulp	*In vitro*	HUVECs	Angiopoietin-1, VEGFA, and ribosomal protein L13a (RPL13a)	PCR and ELISA	Both	No	No	DPMSCs derived from conditioned medium (CM) could enhance capillary tube formation

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
21.	Zhu et al[30]	Dental pulp	*In vivo*	Mice	VEGF and SDF-1α	PCR and ELISA	Both	No	No	Enhanced expression of VEGF and SDF-1α was observed
22.	Li et al[31]	Dental pulp	*In vitro*	Endothelial cell line	VEGF, FGF, ANG-1, and PDGFA	RT-PCR and immunofluorescence	Cells	IGFBP5	No	IGFBP5 overexpression enhanced the expressions of angiogenic differentiation markers
23.	Lu et al[32]	Dental pulp	*In vitro*	Endothelial cell line	p-AKT and cyclin D1	RT-PCR and Western blotting	Cells	VEGF and IGF-1	No	Combined treatment with VEGF and IGF-1 provided a synergistic effect on the angiogenic potential of DPMSCs derived from carious teeth
24.	Youssef et al[33]	Dental pulp	*In vitro*	Endothelial cell line	VEGF	PCR, flow cytometry	Cells	Mineral trioxide aggregate (MTA), calcium hydroxide (Ca [OH]2, Biodentine (BD) and Emdogain	No	The treatment of MTA-enhanced VEGF expression, Ca (OH)2, BD, and Emdogain
25.	Rapino et al[34]	Dental pulp	*In vitro*	Endothelial cell line	EDN1, VEGF, IL–6, and PGE2	ELISA	Cells	Chitlac-coated BisGMA/ triethylene glycol dimethacrylate (TEGDMA) methacrylic thermosets	No	The addition of Chitlac-coated BisGMA/ TEGDMA methacrylic thermosets resulted in tubules with an increased diameter and improved the differentiation of angiogenic cell types

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
26.	Dubey et al[35]	Dental pulp	*In vitro*	Endothelial cell line	VEGF	Light and fluorescence microscopy	Cells	Clindamycin (CLIN) and minocycline (MINO)	HUVECs	There was enhanced cell proliferation and capillary tube formation
27.	Delle Monache et al[36]	Dental pulp	*In vitro*	Endothelial cell line	FGF, VEGF, and EGF	Immunofluorescence, and Western blotting	Cells	Complete endothelial medium 2 (EGM-2)	HUVECs	EGM-2-treated DPMSCs formed tubelike structures that were more stabilized compared to HUVECs alone
28.	Gong et al[37]	Dental pulp	*In vitro*	Endothelial cell line	VEGF	Immunofluorescence microscopy, PCR, and ELISA	Cells	EphrinB2-Fc or EphB4-Fc	HUVECs	EphrinB2-Fc or EphB4-Fc enhanced the DPMSCs to form blood vessels with increased secretion of VEGF
29.	Schertl et al[38]	Dental pulp	*In vitro*	Endothelial cell line	PECAM1, VEGF-A, and KDR	Flow cytometry, and qRT-PCR analysis	Cells	TEGDMA	No	Treatment with 0.25 mM of TEGDMA downregulated angiogenic factor expression, while at 0.1 mM concentration angiogenesis was not affected
30.	Luzuriaga et al[39]	Dental pulp	*In vivo*	Mouse	VEGF	PCR, flow cytometry, and Western blotting	Cells	No	No	Dental pulp–derived cells contributed to the generation of neovasculature in brain tissue
31.	Zou et al[40]	Dental pulp	*In vitro*	Endothelial cell line	VEGF, HIF-1α, ANG1, and ANGPTL4	ELISA	Cells	Sema 4D/plexin B1	No	Signaling through sema 4-D/plexin B1-induced

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
										endothelial differentiation of the DPMSCs
32.	Bindal et al[6]	Dental pulp	*In vitro*	Endothelial cell line	FGF, VEGF-A, HGF, PDGF-BB, MCP-1, and CCL5	RT-qPCR array	Cells	LPS, human platelet lysate (HPL), platelet-rich plasma	No	20% HPL has been shown to provide the most optimal environment to induce proangiogenic factors in inflammatory DPMSCs
33.	Jin et al[41]	Dental pulp	*In vitro*	Endothelial cell line	VEGF, FGF, PDGF, TGF-β	RT-PCR and immunofluorescence	Cells	Concentrated growth factor (CGF) scaffold	HUVECs	At low doses, CGF could potentially stimulate endothelial cell proliferation and migration
34.	Gharaei et al[42]	Dental pulp	*In vitro*	HUVEC line	VEGF, IGF-1, SDF-1, IGFBP-2,3, MMP-9, TIMP-1, and Ang-1	ELISA, RT-PCR, and protein profiling array	Both	No	No	CM released from hDPMSCs can trigger pronounced angiogenic effects
35.	Dou et al[43]	Dental pulp	*In vitro*	Endothelial cell line	VEGFA, HIF-1A, KDR(VEGFR2), TGFβ1, BMP-2, bFGF, HGF, TNF-α, Runx-2, and Notch-1	PCR, flow cytometry, and ELISA	Cells	Hypoxic conditions	No	Hypoxia could promote angiogenesis of the DPMSCs graft via the HIF-1α signaling pathway
36.	Aksel et al[44]	Dental pulp	*In vitro*	Endothelial cell line	VEGF	ELISA and PCR	Cells	Fibrin gel integrated demineralized dentin matrix	No	Increased angiogenic marker expression
37.	Lambrichts et al[45]	Dental pulp	*In ovo* and *in vivo*	Chorioallantoic membrane, mice	VEGF, angiogenin, dipeptidyl peptidase IV, angiopoietin-1, EDN1, IGFBP-3, IL-8, urokinase-	Histopathologic staining	Both	No	No	hDPMSCs significantly augmented blood vessel growth in this ovo model for angiogenesis;

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
					type plasminogen activator, MCP-1					also, pulp vascularization was obtained in a transplanted scaffold in the immune-compromised mice model
38.	Silva et al[46]	Dental pulp	*In vivo*	Mice	VEGF, VEGFR2, and IL-8	ELISA	Cells	Lipoprotein receptor–related protein 6 (LRP6) and Frizzled6, recombinant human Wnt1 (rhWnt1), and recombinant human VEGF165 (rhVEGF165)	No	Lipoprotein receptor–related protein 6 silenced DPMSCs downregulated VEGF expression also showed fewer blood vessel formation in the mice model
39.	Aksel and Huang[47]	Dental pulp	*In vitro*	Endothelial cell line	von Willebrand factor (vWF)	Immunofluorescence	Cells	Endothelial growth medium-2 (EGM-2)	No	EGM-2-induced cells showed improved vessel formation compared to noninduced cells
40.	Zou et al[48]	Dental pulp	*In vitro*	Endothelial cell line	VEGF	ELISA and PCR	Cells	Sema4D/plexin B1	HUVECs	Sema4-D/plexinB1 signaling exerts profound effects on enhancing VEGF secretion and angiogenesis
41.	Nam et al[49]	Dental pulp	*In vivo*	Mice	VEGF, α-smooth muscle actin (α-SMA), PDGF receptor β (PDGFRβ), and CD146	Immunofluorescent staining	Cells	No	HUVECs	
42.	Lee et al[50]	Dental pulp	*In vitro*	HUVECs	VEGF, FGF-2, VEGFRs, PECAM-	PCR	Both	Nanocomposite cements	No	The conditioning with nanocomposite cements-

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
					1, and VE-cadherin					hDPMSC-CM showed the highest tubular number of HUVECs
43.	Lee et al[51]	Dental pulp	*In vitro*	HUVECs	VEGF, PDGF, FGF-2, platelet endothelial cell adhesion molecule 1 (PECAM-1), and VE-cadherin	PCR	Both	Baicalein	No	Baicalein conditioning increased capillarylike tube formation significantly
44.	Spina et al[52]	Dental pulp	*In vitro*	Collagen scaffolds	VEGF and PDGFA	PCR and IHC	Cells	New Zealand Foetal Bovine Serum	No	Expression of *VEGF* and *PDGFA*. hDPMSCs cultured in NZ-FBS were found to produce higher mRNA levels of the said angiogenic factors
45.	Kuang et al[53]	Dental pulp	*In vivo*	Mice	VEGF and HIF-1α	PCR	Cells	Hypoxic conditions	No	After 4 weeks, the hypoxia group significantly enhanced angiogenesis inside the pulp chamber
46.	Shen et al[54]	Dental pulp	*In vivo*	Mice	VEGF, SDF-1, MCP-1, PDGF-BB, IGF-1, TGF-β, and bFGF	IHC, laser Doppler flowmetry	Both	No	No	DP-CM was shown to significantly improve the recovery of persistent blood flow in the ischemic hindlimb of mice
47.	Dissanayaka et al[55]	Dental pulp	*In vivo*	Mice	VEGF	ELISA	Cells	No	HUVECs	The extracellular matrix produced by the DPMSCs promoted the stabilization and

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
										remodeling of capillarylike structures formed by the HUVECs
48.	Boyle et al[56]	Dental pulp	*In vitro*	HUVECs	VEGF	PCR, flow cytometry	Cells	TNF alpha	No	TNF alpha increased the angiogenesis of DPMSCs
49.	Liu et al[57]	Dental pulp	*In vitro*	HUVECs	VEGF, kinase insert domain receptor (KDR), and FGF	Western blotting and RT-PCR	Lentiviral vector-transfected cells	MiR-424	No	Inhibition of miR-424 function promoted endothelial cell differentiation of hDPMSCs, whereas miR-424 overexpression inhibited their angiogenic potential
50.	Bronckaers et al[58]	Dental pulp	*In ovo*	Human microvascular endothelial cell line 1 (HMEC-1), chicken chorioallantoic membrane, mouse brain endothelial cells (MBECs)	VEGF, IL-8, MCP-1, and FGF-2	ELISA and RT-PCR	Both	No	No	An increased number of capillary formations was evident
51.	Janebodin et al[59]	Dental pulp	*In vivo*	Mice	VEGF	PCR	Cells	No	BM-MSCs	DPMSCs' ability to induce vessel formation was more efficient than BMSCs
52.	Ishizaka et al[60]	Dental pulp	*In vivo*	Mice	Granulocyte monocyte colony-stimulating factor (GM-CSF),	Flow cytometry	Both	No	Bone marrow, adipose tissue MSCs	DPMSCs have more significant potential for angiogenesis

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
					matrix metalloproteinase-3 (MMP-3), and VEGF-A					
53.	Dissanayaka et al[61]	Dental pulp	*In vitro*	HUVECs	CD117, VEGF, CD34, and Flk-1	PCR	Cells	No	Endothelial cells	Matrigel assay showed that the addition of DPMSCs stabilized preexisting vessel-like structures formed by endothelial cells and increased their longevity
54.	Iohara et al[62]	Dental pulp	*In vivo*	Mice	VEGF, MMP, CSF, CXCR4, and SDF1/CXCL12	PCR	Cells	No	No	It improved limb ischemia in the hindlimb of the mice model
Stem cells from human exfoliated deciduous teeth (SHED)										
1.	Wu et al[63]	SHED	*In vivo*	Mice	VEGFA, PDGFA, and angiopoietin	RT-PCR	Cells	No	HUVEC and SHED exosomes	SHED exosomes provide expanded possibilities to enhance angiogenesis and pulp regeneration
2.	Han et al[64]	SHED	*In vivo*	Mice	VEGF	ELISA	Both	Transfection of premade siRNA for HIF-1 alpha signal silencing	HUVECs	HIF-1 alpha signaling along with VEGF has a potent role for the use of SHED in regenerative medicine
3.	Zaw et al[65]	SHED	*In vitro*	HUVECs	Bcl-2, NF-κB1, VEGFA, CXCL8, and CXCR1	ELISA, PCR, and flow cytometry	Cells	NF-κB decoy oligodeoxynucleotides (ODNs) or scramble (control)	Human dermal microvascular endothelial cells (HDMECs)	Increased expression of angiogenic factors was observed with co-culture
4.	Atlas et al[66]	SHED	*In vivo*	Mice		Not mentioned	Cells	No	Endothelial cells	

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
					VEGF, HGF, and PDGF-BB					SHED takes part in the prevascularization process to further cause maturation of the vasculature
5.	Guo et al[67]	SHED	*In vivo*	Minipigs	HIF-1a and VEGF	RT-PCR	Cells	No	Regenerated dental pulp stem cells and SHED together (R-SHED), HUVEC	The tube forming parameters on a Matrigel showed highest results for R-SHED. Likewise, the expression of angiogenic markers were higher in R-SHED group compared to the controls
6.	Wang et al[4]	SHED	*In vitro*	HUVECs	VEGF, VEGFR2 CD31 and DLL4	PCR and ELISA	Cells	Treatment with shear stress.	No	Shear stress–induced arterial endothelial differentiation of SHED and VEGF-DLL4/Notch-EphrinB2 signaling was involved in this process
7.	Gong et al[68]	SHED	*In vitro*	HUVECs	VEGF, FGF beta, and hEGF	IHC and PCR	Cells	No	HUVECs and decellularized matrix	Endothelial-induced SHED provided better angiogenesis
8.	Kim et al[69]	SHED	*In vivo*	Mice		PCR and IHC	Cells	No	HUVECs	Co-culture of HUVECs and SHED could provide enhanced angiogenesis *in vivo*
9.	Gorin et al[70]	SHED	*In vivo*	Mice	VEGF, FGF-2, HGF	Flow cytometry ELISA, and IHC	Cells	No	No	SHED has high angiogenic potential that hypoxia further increases

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
10.	Bento et al[71]	SHED	*In vivo*	Mice	VEGF	PCR	Cells	EGM-2MV supplemented with VEGF	No	Increased blood vessel formation
Periodontal ligament–derived mesenchymal stem cells (PDLSCs)										
1.	Iwasaki et al[72]	PDL	*In vitro*	HUVECs	VEGF	ELISA	Conditioned media	No	HUVECs	HUVECs demonstrated minimal apoptotic activity on treatment with PDLSC-CM; increased vascular activity was noted at the same time
2.	Zhang et al[73]	PDL	*In vitro*	HUVECs	CD31 and VEGFA	Flow cytometry	No	No	HUVECs	HUVECs treated with exosomes derived from inflamed PDLSCs exhibited better tube formation than the control group
3.	Diomede et al[74]	PDL	*In vitro*	HUVECs	VEGF and RUNX2	Immunofluorescence and RT-PCR	Cells	Titanium surfaces, machined (CTRL) and dual acid-etched (TEST)	No	Human PDLSCs cultured on TEST evidenced a higher expression of VEGF and RUNX2 than hPDLSCs cultured on the CTRL surface
4.	Marconi et al[75]	PDL	*In vitro*	HUVECs	VEGF, VEGF-R, and RUNX2	Immunofluorescence	Cells	Titanium implant surfaces modified with two different procedures, sandblasted (control—CTRL) and sandblasted/ etched (test—TEST), as	No	TEST surfaces compared to CTRL titanium surfaces enhanced cell adhesion and increased VEGF and RUNX2 expression

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
								experimental titanium surfaces		
5.	Kim et al[76]	PDL	*In vitro*	HUVECs	VEGF, bFGF, and ANGPT1	PCR and Western blot analysis	Both	Cyclosporine A (CsA)	HUVECs	CsA reduced angiogenesis by blocking the ERK and p38/c-fos pathway in hPDLSCs
6.	Iwasaki et al[77]	PDL	*In vivo*	Rat	VEGF, bFGF, and HGF	Flow cytometry and PCR	Cells	No	No	VEGF expression was increased in PDLSCs
7.	Jearanaiphaisarn et al[78]	PDL	*In vitro*	HUVECs	VEGF, alpha-1 type I collagen (COL1), and essential bFGF	qPCR, ELISA, immunofluorescence staining	Cells	Iloprost, prostacyclin receptor (IP) antagonist	No	Iloprost promoted mRNA and protein expression of VEGF and COL1, but not of bFGF in hPDLSCs cells
8.	Wei et al[79]	PDL	*In vitro*	HUVECs	bFGF and Ang	PCR and flow cytometry	Cells	No	PDLSCs from healthy teeth and periodontally compromised teeth, rapamycin, and cDNA-Beclin-1	Proangiogenic cytokine expression increased, and more tube formation was observed in periodontally compromised teeth derived PDLSCs
9.	Bae et al[80]	PDL	*In vivo*	Mice	Stromal cell–derived factor 1 (SDF-1)	PCR and immunofluorescent	Cells	CXCR4 antagonist	HUVECs	Co-injection of PDLSCs and HUVECs worked up well for establishing vascular anastomosis
Stem cells from apical papilla (SCAPs)										
1.	Yi et al[81]	SCAPs	*In vivo*	Mice	CD31, VEGFR2, VEGFR1, and TIE2	RT-PCR, western blotting, flow cytometry, and	Cells	Acetylated low-density lipoprotein (ac-LDL)	HUVECs, SCAPs-endothelial cells	Angiogenic factors enhanced the differentiation of SCAPs

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
						immunofluorescence				into endothelial cells
2.	Liu et al[82]	SCAPs	*In vitro*	Endothelial cell lines	Hypoxia-inducible factor-1α (HIF-1α) and VEGF	RT-PCR and ELISA	Both	Cobalt-doped multiwalled carbon nanotube nanocomposites	Endothelial cells	Conditioned media collected from SCAP when treated with nanocomposites showed enhanced vessel formation
3.	Yu et al[83]	SCAPs	*In vitro*	HUVECs	VEGF and FGF-2	RT-PCR and immunofluorescence staining	Both	No	BM-MSCs, dental pulp cells (DPCs)	SCAPs-CM showed enhanced osteogenic and neurogenic differentiation in DPCs but did not prove to be significant in angiogenesis
4.	Yuan et al[84]	SCAPs	*In vivo*	Mice	VEGF	PCR and ELISA	Cells	SCAPs transduced with an ephrinB2-lentiviral expression vector (ephrinB2-SCAPs) in the experimental group and green fluorescent protein (GFP-SCAPs) in the control group	HUVECs	Enhanced expression of VEGF was observed with ephrinB2 transduction
5.	Koutsoumparis et al[85]	SCAPs	*In vitro*	HUVECs	PECAM-1, VEGFR2, vWF, and VE-cadherin/CDH5 MMP-2	RT-PCR and flow cytometric analysis	Cells	Recombinant human erythropoietin-alpha (rhEPOa)	No	rhEPOa is capable of promoting endothelial transdifferentiation of SCAP
6.	Yadlapati et al[86]	SCAPs	*In vivo*	Mice	Left-right determination factor 1 (LEFTY1), bone morphogenetic	ELISA	Cells	VEGF loaded (concentration of 12.2 ng/cm) polydioxanone fiber	No	Accelerated angiogenesis was achieved

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
					protein 8b (BMP8B), peptidylprolyl isomerase A (PPIA), bone morphogenetic protein 4 (BMP4), TGFβ1, FGF5, colony-stimulating factor 1 (CSF1), VEGFC, pleiotrophin (PTN), and ubiquitin C (UBC), VEGFA, PPIA, chemokine (C-X-C motif) ligand 1 (CXCL1), hydroxymethylbilane synthase (HMBS), RPL0, and inhibin beta A (INHBA)					
7.	Yuan et al[87]	SCAPs	*In vitro*	HUVECs	VEGF	PCR and ELISA	Cells	EphrinB2	HUVECs	Co-culture of SCAPs and HUVECs accelerated the formation of vascularlike structures while inhibition of EphrinB2 expression suppressed the formation of vessel-like structures
8.	Peters et al[88]	SCAPs	*In vitro*	HUVECs	VEGF, ANGPT1, c-fos0-induced growth factor (FIGF), FGF2, and TGFβ1	Flow cytometry and PCR	Cells	ProRoot MTA or BD	No	VEGF expression was enhanced by stimulating either MTA or BD types of cement, but FGF and ANGPT1

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
										expression were reduced
9.	Bakopoulou et al[89]	SCAPs	*In vitro*	HUVECs	Angiogenin, IGFBP-3, VEGF, PDGF, IGF1, MMPs, PECAM-1, and VE-cadherin	PCR, flow cytometry, and ELISA	Both	SCAP was exposed to serum deprivation (SD), glucose deprivation (GD), and oxygen deprivation/ hypoxia (OD) conditions	HUVECs	Exposing the cells to stressed conditions proved to enhance the angiogenesis obtained from CM
10.	Yuan et al[90]	SCAPs	*In vitro*	HUVECs	VEGF, EphrinB2, angiopoietin, EphB4, insulin growth factor-1, EDN1, FGF, PDGF, and TGF-β	ELISA and RT-PCR	Cells	Hypoxic conditions	HUVECs	HIF-1a and ephrinB2 in SCAP under hypoxia are upregulated
Gingival mesenchymal stem cells (GMSCs)										
1.	Jin et al[91]	GMSCs	*In vivo*	Mice	VEGF-A, TGF-β, and FGF-2	ELISA and RT-PCR	Both	Lentivirus transfection and FGF-2	HUVECs	FGF-2 gene-modified GMSCs constructed using lentiviral transfection promoted GMSCs paracrine of angiogenesis-related growth factors
Comparison of OC-MSC sources										
1.	Zhu et al[92]	SHED and DPSC	*In vitro*	HUVECs	PDGFR-β, α-SMA, NG2, and DEMSIN	RT-PCR	Cells	No	HUVECs	DPSCs performed better as a candidate in angiogenic assays compared to SHED
2.	Xie et al[93]	SHED and DPMS-C	*In ovo*	Chick embryo CAM	PECAM-1/CD31, VEGF, VEGF receptor 1 (VEGFR1), VEGF	RT-PCR	Cells	No	BM-MSCs	Angiogenic gene expressions were increased in SHED compared

(*Continued*)

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
					receptor 2 (VEGFR2), and vWF					to DPMSCs or BM-MSCs
3.	Angelopoulos et al[94]	Gingival MSCs (GMSCs) and DPMSCs	*In vivo*	Mice	VEGF and HGF	Flow cytometry, ELISA, and IHC	Both	No	No	GMSCs showed an improved angiogenic capacity compared to DPMSCs
4.	Xu et al[95]	DPMSCs and SHED	*In vivo*	Mice	VEGF-A, VEGF-RI, PlGF-1, TGF-β, and SB-431542	RT-PCR and IHC	Cells	No	No	SHED possessed a higher endothelial differentiation potential than DPMSCs
5.	Osman et al[96]	PDLSCs and SHED	*In vitro*	HUVECs	TGF, IGF, FGF, VEGF, PDGF, and CTGF	PCR	Cells	No	No	PDLSCs showed a higher propensity toward angiogenesis compared to DPMSCs
Combined sources of stem cell										
1.	Zhang et al[97]	DPSCs and SHED	*In vivo*	Mice	VEGFR2, Tie-2, CD31, and VE-cadherin	Flow cytometry	Cells	No	No	p53/p21 regulates the angiogenic potential of DPSCs and SHED *in vivo*
2.	Olcay et al[98]	DPMSCs, PDLSCs, and human tooth germ stem cells (hTGSCs)	*In vitro*	HUVECs	FGF-2, PDGF, and VEGF	Flow cytometry and ELISA	Both	Tricalcium silicate-based MRA (ProRoot MTA), BD, and a novel bioceramic root canal sealer (Well-Root ST) and Dycall are positive control groups	HUVECs	VEGF levels were significantly higher in a ProRoot MTA group

Table 1 (*Continued*)

Sl. no.	Study	Source of stem cells	Type of study	Model used	Factors assessed for angiogenesis	Method used for analysis	Use of stem cells/ conditioned media	Use of preconditioning (yes/no)	Use of co-culture with MSCs (yes/no)	Results obtained
3.	Hilkens et al[99]	DPMSCs and SCAPs	*In vivo*	Mice	VEGF, primary bFGF, angiopoietin-1, MMPs, endostatin, thrombospondin-1, and IGFBP3	ELISA and IHC	Cells	No	No	Co-culture of DPMSCs and SCAPs provided enhanced angiogenic proliferation of cells and improved blood vessel growth *in vivo*
4.	Zhang et al[100]	DPMSCs and SHED	*In vivo*	Mice	VEGF, Wnt-β-catenin	PCR and IHC	Cells	No	No	Wnt/b-catenin silencing depressed angiogenesis by DPMSCs
5.	Hilkens et al[101]	SCAPs and DPMSCs	*In ovo*	Chorioallantoic membrane	VEGF, bFGF, HGF-1, ANGPT1, and IGFBP3	PCR and ELISA	Both	No	No	DPMSCs and SCAPs caused a significant increase in blood vessel count

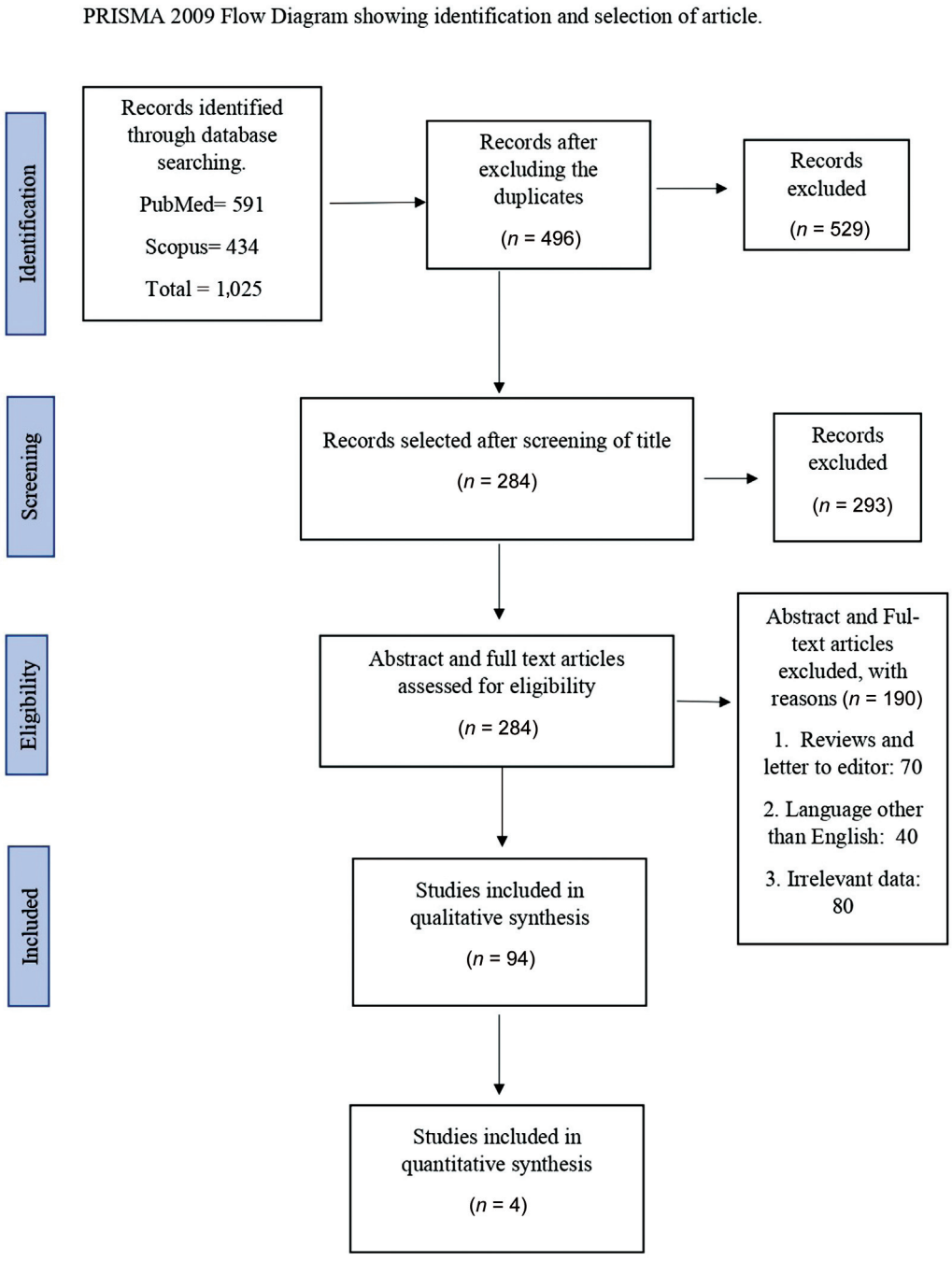

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart illustrating the research methodology used in the review.

strategy employed in the qualitative and quantitative analysis is illustrated using the PRISMA flowchart. The results of database searches were carefully maintained using Mendeley software (version 1803). Mendeley software (version 1803) for Windows (Elsevier, London, UK) was used in the initial phase of the screening process to remove duplicate articles. Five hundred and twenty-nine articles from both databases were excluded due to overlapping data. After scrutiny of the titles, 284 articles were selected. Abstracts and full texts of the remaining articles were further screened for relevance, and 80 articles were excluded. In addition, 70 reviews and letters to editors were excluded. Of the remaining 134 articles, 40 were excluded due to data being in languages other than English or irrelevance. Hence, a total of 94 articles were selected for data extraction. The data extracted from the included studies are summarized in ►**Table 1**. ►**Fig. 1** summarizes and depicts the PRISMA flowchart. Source-wise number of articles included in the review are depicted in the graph in ►**Fig. 2**.

A quantitative analysis was possible only for comparing studies with an individual oral-derived source of MSCs. The DPMSCs and SCAPs were individually compared with the endothelial cell lines used to control *in vitro* analysis of blood vessel formation. Thus, the best source of oral-derived MSCs

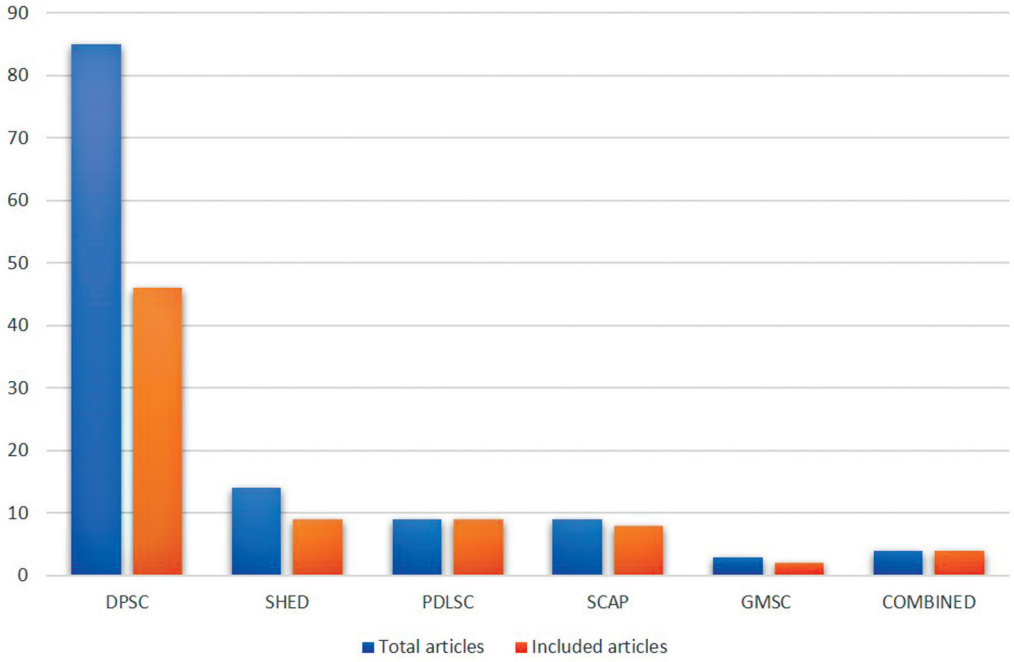

Fig. 2 Graphical representation of the source-wise articles included in the review. DPSC, dental pulp stem cell; GMSC, gingival mesenchymal stem cell; PDLSC, periodontal ligament–derived mesenchymal stem cell; SCAP, stem cells from apical papilla; SHED, stem cells from human exfoliated deciduous teeth.

is not projected through the meta-analysis performed. Instead, the present meta-analysis shows that oral tissue–derived stem cells have more potential for augmenting angiogenesis than endothelial cell lines alone. The studies compared the *in vitro* tubule formation or total branching points between cases and controls. Out of the 94 studies in the systematic review, only four had data compatible with a meta-analysis.[34,61,84,90] These studies referred to tubular formation's mean and total branch points in the case and control groups. The difference between the mean with standard deviation and the corresponding confidence interval was calculated for each study. Forest plots were created with RevMan software (version 5.4.1) using the calculated mean differences shown in ►**Figs. 3**–**5**.

The meta-analysis (►**Fig. 3**) shows a positive correlation of the co-culture of human umbilical vein endothelial cells (HUVECs) and DPMSCs with tubule length formation, which was statistically significant ($p = 0.04$), with a mean difference of 0.20 and a 95% confidence interval of 0.01–0.40. Succeeding meta-analysis (►**Figs. 4** and **5**) showed a positive correlation with the co-culture of HUVEC and the SCAP group with tubule length formation (►**Fig. 4**) and total branching points (►**Fig. 5**) with a mean difference of 5.20 and 20.78 and a 95% confidence interval of −2.05 to 12.45 and −6.66 to 48.21, respectively. Thus, the overall results from the meta-analysis revealed that oral-derived MSCs (DPSC and SCAP) carry a better angiogenic potential *in vitro* than the endothelial cell lines used alone, as depicted in the forest plot in ►**Figs. 3**–**5**.

Assessment of Quality and Publication Bias

Ten of the 94 studies considered obtained ratings less than 70%, categorizing them as intermediate in quality. In contrast, the other 84 studies were classed as high quality given that their overall score surpassed 70%. The studies included for meta-analysis were high quality with score greater than 70%.

The Egger test showed a potential publication bias with 50% studies closer to the intercept line and 50% of studies away from the intercept line (►**Table 2**, ►**Fig. 6**). Such skewed results could be attributed to small sample of studies that were analyzed quantitatively.

Discussion

After a detailed scrutiny of the literature, 94 articles meeting our inclusion criteria were included in the review, investigating the influence of MSCs or their secretomes derived from oral sources. Of these, 54 studies involved dental pulp, 10 articles investigated MSCs from SHED, and 9 investigated the PDL stem cells. The SCAPs were studied in 10 articles, and gingival MSCs (GMSCs) were explored in a single study. DPMSCs were relatively more explored for their angiogenic potential, as evidenced by the number of articles published. The critical parameters investigated to assess the effect of OC-MSCs and their secretomes on angiogenesis were tube capillary length and diameter, branching points, number of loops, expression of angiogenic proteins, endothelial cell proliferation in *in vitro* studies and capillary formation, enhanced wound healing, and generation of neovascularization in *in ovo* and *in vivo* studies. Postnatal MSCs (DPMSCs, PDL-derived stem cells [PDLSCs], SHED, GMSCs, and SCAP) retain the unique ability to form new functional blood vessels through angiogenesis.[97]

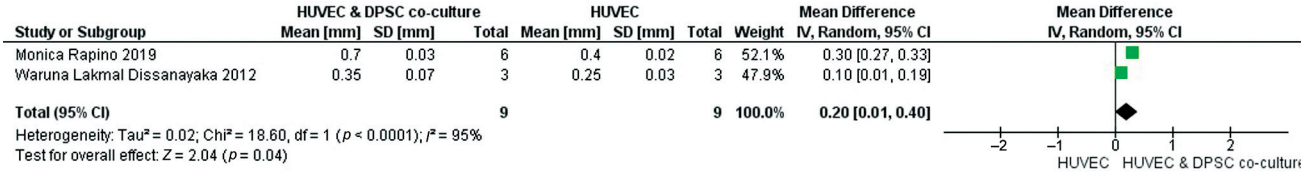

Fig. 3 Summary of the meta-analysis assessing the effect of DPMSCs on the tubular length in an *in vitro* Matrigel assay showing a positive correlation of the co-culture of HUVEC and DPMSCs with the tubule length formation, which was statistically significant ($p = 0.04$). CI, confidence interval; DPMSCs, dental pulp–derived mesenchymal stem cells; DPSC, dental pulp stem cell; HUVEC, human umbilical vein endothelial cell; SD, standard deviation.

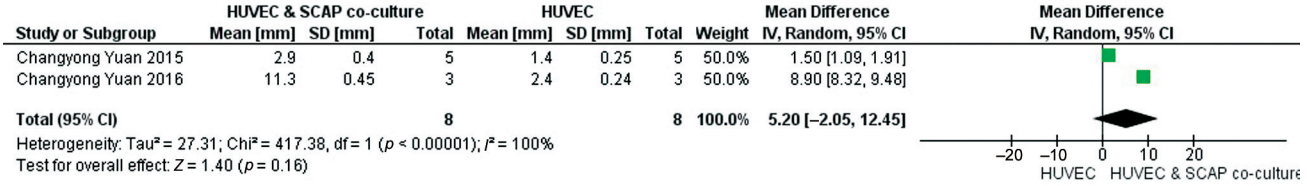

Fig. 4 Summary of the meta-analysis assessing the effect of SCAP on the tubular length in an *in vitro* Matrigel assay showing a positive correlation of the co-culture of HUVEC and SCAPs with the tubule length formation, which was not statistically significant ($p = 0.16$). CI, confidence interval; HUVEC, human umbilical vein endothelial cell; SCAP, stem cells from apical papilla; SD, standard deviation.

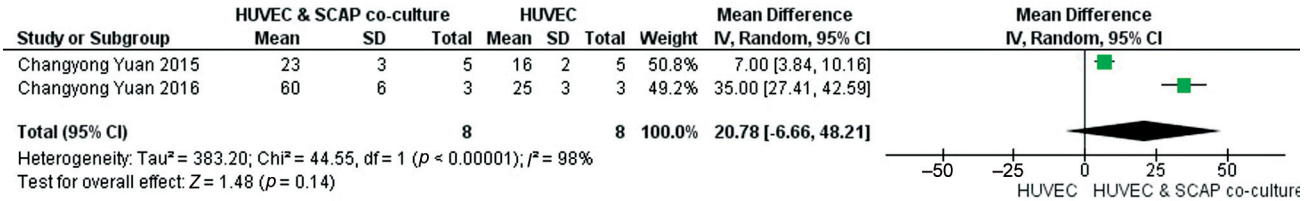

Fig. 5 Summary of the meta-analysis assessing the effect of SCAP on the total branching points in an *in vitro* Matrigel assay showing a positive correlation of the co-culture of HUVEC and SCAPs with the total branching point number, which was not statistically significant ($p = 0.14$). CI, confidence interval; HUVEC, human umbilical vein endothelial cell; SCAP, stem cells from apical papilla; SD, standard deviation.

Table 2 Tabular representation of Egger's regression test

Study reference	*Z*-score	SD	*n*	SE	1/SE
2012	2.27	0.7	3	0.404	2.474
2015	7.11	0.4	5	0.179	5.590
2016	30.23	0.45	3	0.260	3.849
2019	20.38	0.03	6	0.012	81.650

Abbreviations: SD, standard deviation; SE, standard error.

Dental Pulp–Derived Mesenchymal Stem Cells

The dental pulp is a rich source of MSCs that exhibit a self-renewal multilineage differentiation potential and secrete multiple proangiogenic factors. Thus, among the several therapeutic applications under investigation, the ability of DPMSCs to enhance angiogenesis has been the subject of active investigation.

Interestingly, the co-culture of DPMSCs with HUVECs exhibited a thick vessel-like structure, a characteristic feature of angiogenesis. The formation of vessel-like structures was absent in untreated HUVECs, confirming the angiogenic role of DPMSCs.[55,61] DPMSCs could induce angiogenesis in a chicken chorioallantoic membrane model, as shown by the increased capillaries that observe a typical spoke wheel pattern around the DPMSCs Matrigel.[58] DPMSCs mediated noticeable repair of the infarcted myocardium in the animal model of myocardial infarction as an increase in the total number of blood vessels and an overall reduction in the infarct size was apparent. Therefore, the authors suggested DPMSCs as a potential alternative to bone marrow–derived MSCs to treat myocardial infarction.[59,102] DPMSC-derived cells could promote neovasculogenesis in the mouse brain.[39]

Secretomes derived from DPMSCs have been actively investigated for their proangiogenic role. DPMSC secretomes

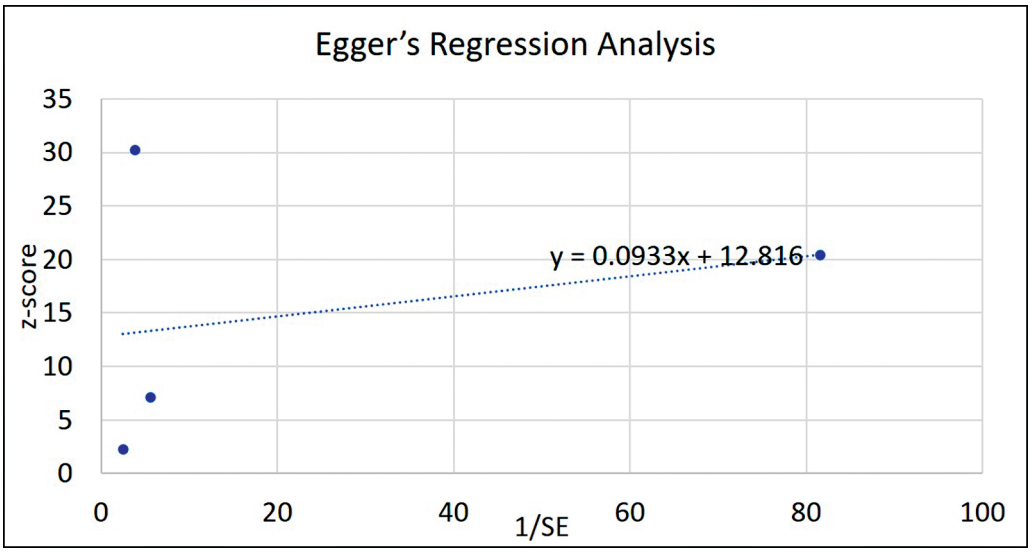

Fig. 6 Graphical representation of Egger's regression test.

also potentially enhance the proliferation of HUVECs.[24] DPMSC secretomes promoted angiogenesis in endothelial cell progenitors and terminally differentiated endothelial cells, as evidenced by the formation of tubelike structures in the Matrigel assay. In addition, DPMSC secretomes have been shown to improve the capillary density of skeletal muscles through improved angiogenesis, which can be attributed to the VEGF content in the secretomes. In the transwell migration assay performed on HUVECs, DPMSC secretomes promote better migration of HUVECs and microvascular network formation than the endothelial growth medium (EGM), suggesting a profound angiogenic role of DPMSC secretomes.[42] Under serum-free conditions, DPMSC secretomes have been shown to enhance the capillary tubelike formation from preexisting blood vessels, ultimately assisting angiogenesis.[29]

In a co-culture of secretomes derived from DPMSCs and bone marrow–derived MSCs, substantial proangiogenic changes were observed in the chorioallantoic membrane.[22] Furthermore, local intramuscular injection of DPMSC secretomes in the hindlimb ischemic mice model showed enhanced neovascularization and marked improved blood perfusion at the ischemic site.[54,60,62] Similar results were found in a mice model of ectopic tooth transplantation wherein enhanced expression of VEGF was noted, promoting pulp regeneration.[30,77] Furthermore, DPMSC secretomes could promote pulplike vascularization in a scaffold implanted in a mouse model.[45]

One of the added therapeutic benefits of MSCs is their ability to secrete EV containing various nucleic acids, lipids, and proteins into the extracellular space. Many studies have suggested that EVs from MSCs can be employed for therapeutic applications in recent times. Interestingly, fibrin gel loaded with DPMSC-derived EVs enhanced cell migration and vascular tube formation in *in vitro* culture.[27] A mouse model was used to assess wound healing over the skin, where EVs derived from DPMSCs of healthy and periodontally compromised teeth were included. The results showed that EVs from DPMSCs from periodontally compromised teeth (P-DPMSCs) accelerated wound healing in mice compared to those derived from DPMSCs from healthy teeth.

Moreover, it showed enhanced blood vessel formation/angiogenesis, which forms the basis of wound healing, suggesting that the inflammatory microenvironment enhances the proangiogenic effects of DPMSCs. A comparative analysis between the DPMSCs derived from regular and deep carious teeth revealed that the expression levels of angiogenesis markers (VEGF, PDGF, stromal cell–derived growth factor-1) were higher in MSCs derived from deep carious pulp compared to the MSCs of the normal pulp. This suggests that an inflammatory microenvironment would instead work well for cell proliferation and further angiogenesis.[25] A combination of VEGF and IGF-1 enhances the angiogenic proliferation of DPMSCs from the carious environment synergistic effect.[32] Chronic inflammation-mediated tumor necrosis factor alpha induced initial apoptosis emerges DPSC into an angiogenic phenotype.[40,56] The role of DPMSC EVs in angiogenesis is evident as miR-424 plays a regulatory role in angiogenesis.[57] Recently, modulation of the proangiogenic potential of DPMSCs by preconditioning, altering the culture conditions, and using novel biomaterials yielded promising results. Hypoxic preconditioning could enhance the proangiogenic capacity of DPMSCs.[43,53] The expression of HIF-1α and SENP1 formed a positive feedback loop in angiogenesis promoted by DPMSCs under hypoxic conditions. HUVECs cultured with DPMSC secretomes treated with baicalein,[51] calcium phosphate cement (CPC), and CPC-bioactive glass nanoparticles (CPC-BGNs),[50] insulin-like growth factor binding protein 5 (IGFBP5)[10] exhibited higher expression of angiogenic markers in DPMSCs. DPMSCs treated with mineral trioxide aggregate (MTA), calcium hydroxide (Ca [OH]2), Biodentine (BD) and Emdogain,[23] EphrinB2-Fc, or EphB4-Fc[37] enhanced the expression of VEGF, which plays a crucial role in angiogenesis.[52]

In contrast, treatment with triethylene glycol dimethacrylate (TEGDMA) alone at a concentration of 0.25 mM

downregulated the expression of angiogenic factors,[38] clindamycin and minocycline[35]; complete endothelial medium 2 (EGM-2) improved vessel formation; and angiogenic cell differentiation was achieved.[36] Aksel and Huang observed similar findings.[47] Treatment with 20% human platelet lysate under lipopolysaccharide-induced inflammatory environment in DPMSCs showed increased expression of proangiogenic markers.[6] Furthermore, the concentrated growth factor scaffold potentially enhanced endothelial cell proliferation and migration for DPMSCs.[41] Lipoprotein receptor–related protein signaling is required to express VEGF-promoting angiogenesis.[46] Decellularized matrix hydrogel derived from human dental pulp effectively promoted DPMSCs in a multidirectional differentiation.[31]

Stem Cells Obtained from Exfoliated Deciduous Teeth

SHED is a potent source of MSCs due to their higher proliferation potential, plasticity, and unique secretory profile. Few studies have explored the ability of SHED to enhance angiogenesis. Co-culture of the SHED with HUVECs promoted increased angiogenesis.[68] Furthermore, the SHED-HDMEC co-culture enhanced proangiogenic factor expression via NF-κB-dependent pathways.[65] Interestingly, SHED was subjected to shear stress-induced arterial endothelial differentiation.[4] SHED supplemented with an EGM showed augmented angiogenesis *in vivo*.[71] When subjected to a hypoxic environment, SHED augmented angiogenesis with improved function.[70] These studies suggest that SHED can be used as a perivascular source to form functional vascularlike structures *in vivo*.[76]

Periodontal Ligament–Derived Stem Cells

The PDL contains a population of progenitor cells, recently recognized as PDLSCs, capable of multilineage differentiation to produce tissues rich in collagen type I. Coadministration of PDLSCs and HUVECs showed anastomosis and enhanced blood vessel formation. It was seen that CXCR4 (an alpha-chemokine receptor specific for stromal-derived factor 1) antagonist inhibited blood vessel formation. This explains the role of PDLSCs in augmenting angiogenesis and blood vessel formation.[80] Furthermore, PDLSCs seeded on machined titanium disk surfaces showed increased VEGF expression, and RUNX2 (a gene inducing pluripotent stem cell differentiation to immature osteoblasts) plays a potential role in exhibiting angiogenesis.[74] In contrast, cyclosporine A–treated MSCs derived from PDL negatively impacted angiogenesis.[76]

Furthermore, prostacyclin pretreated PDL stem cells negatively impacted iloprost enhanced angiogenic marker expression.[78] PDLSCs derived from healthy and inflamed tissue (periodontally compromised teeth) were subjected to proliferation and angiogenesis. The results depicted that the inflammatory microenvironment provided better augmentation for angiogenesis, which agrees with the findings on DPMSCs.[73,79]

Stem Cells Derived from Apical Papilla

A unique population of SCAP of the growing tooth root tips with embryoniclike properties is readily accessible in dental clinical practice from extracted wisdom teeth. Exposure of SCAP to various stress microenvironments and their respective secretomes has promoted angiogenesis.[89] EphrinB2 (a transmembrane ligand of EphB receptor tyrosine kinases expressed explicitly in arteries) could stabilize the vessel-like structure generated by the co-culture of SCAPs and HUVECs *in vitro*.[87] Co-culture of HUVECs and SCAPs under hypoxic conditions promoted the formation of endothelial tubules and a blood capillary network, which was in agreement with those obtained by Nam et al.[49] VEGF-loaded fibers can be considered a viable option for stimulating SCAP angiogenesis and new histogenesis during the endodontic procedure.[86] EphrinB2-transduced SCAPs could express VEGF marker in numerous amounts compared to the control group; its co-culture with HUVECs showed enhanced blood vessel formation in a Matrigel plug assay.[84] Treatment of SCAP cells with recombinant human erythropoietin-alpha (rhEPOa) elicits a proangiogenesis program by activating the Erythropoetin Receptor pathway.[85] Exposure of SCAP to MTA and BD (root-end filling material used in endodontic therapy of root canals) stimulated angiogenic gene expression and VEGF release inducing similar expression patterns in both MTA and BD. However, they appear to inhibit the expression of specific genes, including ANGPT1 and FGF2.[88] SCAP-derived secretomes improved osteogenic and neurogenic differentiation of dental pulp cells, but angiogenic differentiation did not significantly improve.[83]

Stem Cells Derived from Gingiva

The gingiva of human dentition is blessed with a remarkable contribution of neural crest ectomesenchyme, perifollicular mesenchyme, and partly the dental follicle proper. The origin of this tissue and its close approximation with the tooth give the GMSCs an exclusive position to stand apart from the rest of the oral cavity–derived cells. A study by Jin et al showed that when GMSCs were transfected with FGF-2, their expression potential for VEGF and TGF-β increased. Also, the secretomes derived from untreated GMSCs enhanced the gene and protein expression of angiogenic-related factors, endothelial tube formation, and cell migration capacity. However, the results obtained had an inferior efficacy than those obtained by the transfected GMSCs and their secretomes.[91]

Several researchers have investigated the comparative potential of OC-MSCs to explore the ideal source of MSCs in the augmentation of angiogenesis. In a study by Angelopoulos et al, GMSCs potentially proliferate, migrate, and form angiogenic tubules better than DPMSCs *in vitro* and *in vivo*.[94] Another study performed by Xu et al compared SHED and DPMSCs in enhancing angiogenesis. Their findings revealed that SHED possesses better angiogenic potential than the DPMSCs.[95] Furthermore, SHED showed a more substantial angiogenesis differentiation and proliferation potential than DPMSCs. Furthermore, PDLSCs exhibited better angiogenic potential than DPMSCs.[96] However, very few studies have reported the comparative potential of OC-MSCs.

In yet another study, a co-culture of DPMSCs and SCAPs exhibited improved blood vessel formation *in vivo*.[99]

Furthermore, in an *in ovo* angiogenesis assay, the co-culture of DPMSCs and SCAPs showed better angiogenesis than the single source.[101] A root canal obturating material, Well-Root ST stimulated neovascularization during endodontic regeneration procedures. Furthermore, Well-Root ST showed better efficacy than BD or ProRoot MTA for stimulation in various oral-derived MSCs (DPMSCs, SHED, PDLSCs, GMSCs, and SCAP).[98]

The field of oral cavity–derived stem cells, particularly MSCs from dental pulp and apical papilla, has garnered interest due to their unique characteristics and potential applications in regenerative medicine. The finding that these stem cells have strong angiogenic potential holds several clinical implications and suggests promising directions for future research that could benefit the population in various ways.

- *Tissue regeneration:* The angiogenic potential of oral cavity–derived stem cells suggests their capability to stimulate the formation of new blood vessels. This can be extremely valuable in regenerating damaged tissues, such as those affected by injury, disease, or degeneration. These stem cells could aid in promoting blood supply and nutrients to the regenerating tissue, enhancing the overall healing process.
- *Wound healing:* The ability of these stem cells to promote angiogenesis can significantly accelerate wound healing in various clinical scenarios. For instance, they could be employed in chronic wound management, diabetic ulcer treatment, and postsurgical wound healing to expedite tissue repair and reduce complications.
- *Bone regeneration:* Oral-derived MSCs have shown potential for bone tissue regeneration. Enhancing angiogenesis could aid in developing more effective treatments for bone defects, fractures, and conditions like osteoporosis.
- *Dental applications:* The dental pulp and apical papilla are easily accessible sources of MSCs. This accessibility could make these stem cells valuable for various dental applications, such as periodontal tissue regeneration, dental implant support, and treatment of oral diseases.
- *Cardiovascular disorders:* Given their angiogenic properties, these stem cells might hold promise in treating cardiovascular diseases. They could stimulate the growth of new blood vessels in ischemic heart tissue, potentially reducing the impact of heart attacks.

Limitations

The current literature shows a paucity of studies involving sources other than dental pulp. Even though OC-MSCs have proved their enhanced potential compared to other MSCs, further target-oriented comprehensive research is required to conclude which oral-derived stem cells have the most significant angiogenic potential. The systematic review involves different oral sources for MSCs, where maximum studies include dental pulp, and data for other sources (SHED, PDLSC, SCAP, and GMSC) are limited; therefore, a comparative evaluation could not be done. This systematic review incorporates *in vitro*, *ex vivo*, and *in vivo* trials and the data appear to be skewed. One specific type of research design might be advocated for better outcomes.

Conclusion

The specific objectives of our study were to explore whether easily accessible OC-MSCs from dental pulp and apical papilla had good angiogenic potential. The reviewed literature shows that all the OC-MSCs augmented angiogenesis in various experiments. In the studies comparing DPMSCs and PDLSC, GMSCs, or SHED, the latter sources have shown increased significant potential for angiogenesis compared to that of the DPMSCs. MSCs obtained from different places show close phenotypic characteristics. However, it is still unclear how similar they are since proliferation and differentiation capabilities in the presence of different growth factor stimuli differ depending on the source of origin. For instance, bone marrow MSCs tend to lose their proliferative potential with age. DPSCs, on the other hand, have a higher proliferation index and growth potential. DPSCs show the highest odontogenic capability under the same inductive microenvironment in comparison to bone marrow stromal stem cells.[103]

Avenues that can be explored further in the research realm are angiogenesis mechanisms, optimal delivery methods, combination therapy, and personalized medicine. This knowledge of precise molecular and cellular mechanisms underlying the angiogenic potential of oral-derived MSCs could lead to the development of targeted therapies. Future research could focus on identifying the most effective methods for delivering oral-derived MSCs to target tissues. This could involve investigating various delivery vehicles, such as scaffolds or hydrogels, to ensure the stem cells reach their intended destination. Furthermore, research might delve into tailoring treatments based on individual patient characteristics to maximize the regenerative potential. Exploring combination therapies, such as coupling oral-derived MSCs with growth factors or other regenerative agents, could enhance their angiogenic potential and effectiveness in various applications. Regenerative medicine and stem cells will usher in a renaissance in therapy in the near future.

The manuscript has been checked with the Fi-index tool and obtained a scrore of 0.60 for the first author on September 3, 2023 according to the Scopus database. The Fi-index tool aims to ensure the quality of the reference list and limit autocitations.[104,105]

Authors' Contribution

All the authors contributed to the concept and design of the study.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

Conflict of Interest

None declared.

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