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The Regenerative Power of Umbilical Cord Stem Cells Encapsulated in Bio scaffold in Endodontics: A Systematic Review

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ABSTRACT

Objectives: To evaluate the potential of regenerative endodontic therapy using umbilical cord mesenchymal stem cells (UCMSCs) embedded within an artificial scaffold as a replacement for traditional endodontic treatment techniques.

Materials and Methods: Studies from January 2013 to August 2025 were extracted using four databases (PubMed, ProQuest, EBSCO, and Science Direct).

Results: Eight studies evaluated the efficacy of various scaffolds and growth medium in pulpal regeneration utilizing umbilical cord stem cells. Numerous scaffolds were used, including Platelet-Poor Plasma scaffolds (PPP), alginate hydrogels containing transforming growth factor beta (TGF), Gelatin methacrylate hydrogels (GeIMA), Peptide hydrogel scaffolds, Liquid extract of human treated dentin matrix (LE-TDM) matrix and extracellular matrix incorporated into hydrogels, metrigel hydrogel and tooth germ cell conditioned medium (TGC-CM).

Conclusions: According to the findings, UC-MSCs encapsulated in a PPP matrix and matrigel hydrogel scaffolds provide a unique, safe, and highly successful approach for regenerative endodontics, whereas other scaffolds and cultures demonstrated only minimal regeneration of the pulp. However, further randomized clinical trials with standardized protocols are necessary to validate their widespread clinical application.

Keywords: Umbilical cord, Stem cell therapy, Pulp regeneration, Scaffolds.

1. Introduction

Research shows that a variety of trustworthy mesenchymal stem cell (MSC) sources, such as adipose tissue, bone marrow, or umbilical cord, may be used to build tooth structures using stem cell-based therapeutic techniques (1,2). MSCs derived from human umbilical cord tissue have demonstrated great promise (1). Despite its vital role in supplying teeth with nutrients and nerves, dental pulp tissue is particularly vulnerable to chemical, mechanical, thermal, and microbiological damage. Endodontic therapy that does not restore pulpal vitality to necrotic teeth can be replaced by regenerating the pulp tissue (3). Moreover, the current philosophy is based on instrumentation, disinfection, obturation and root canal filling (4). The use of cell-based treatments in the management of endodontic rejuvenation and revitalization has been demonstrated in several *in vitro* and *in vivo* investigations (4,5).

Owing to their high proliferative capacity, multi-lineage differentiation potential, reduced risk of viral contamination due to the placental barrier, and ability to develop into odontoblasts and other specialized cells,

umbilical cord mesenchymal stem cells (UC-MSCs) have been selected as a favorable source for this research (6). Importantly, UC-MSCs exhibit strong osteogenic, angiogenic, and immunomodulatory properties, making them particularly suitable for regenerating complex tissues, such as the pulp-dentin complex (14). Studies have shown that UC-MSCs can express odontoblast-like and endothelial markers, form vessel-like structures, and regenerate pulp-like tissue when co-cultured, highlighting their potential as a versatile tool in endodontic regeneration (14).

However, the histological structure of dental pulp is a complex, highly organized multi-cellular system that includes fibroblasts, odontoblasts, immune cells, and a rich vascular network. As a result, finding an effective scaffold for pulp tissue regeneration or engineering remains of critical importance. Scaffolds must offer the right conditions for cell survival, recruitment, and adhesion (7). They are broadly classified into natural and synthetic categories, with examples of natural scaffolds including collagen and platelet-derived matrices (8). For pulpal regeneration in mature permanent teeth, this systematic study evaluated the effectiveness of encapsulated human UC-MSCs and their capacity to differentiate into the dentinogenic pathway.

2. Materials and Methods

2.1 Protocol Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Prospective International Register of Systematic Reviews (PROSPERO) (ID: CRD42020219547).

2.2 Search Strategy

As a search approach, both internet and offline browsing were employed to locate literature. EBSCO, ProQuest, PubMed, and Science Direct were all scoured for relevant information. The search for encapsulated umbilical cord stem cells using various bio scaffolds and their potential in regenerative endodontics was conducted from January 2013 to August 2025. "Umbilical cord" AND/OR "stem cells" AND "Endodontics" AND/OR "Pulp regeneration" were the most used terms across all databases. Searching for peer-reviewed and full-text papers was made easier by the inclusion of these databases' filters.

2.3 Inclusion and Exclusion Criteria

An investigation of studies on pulp regeneration utilizing umbilical cord stem cells published after 2013 was conducted. Human umbilical cord mesenchymal stem cells (hUCMSCs) may be differentiated into odontoblasts in the laboratory using platelet-poor plasma (PPP) scaffold or dentin matrix scaffold and tooth germ cells–conditioned media (TGC-CM). English-language papers were included. Studies using other kinds of stem cells, different scaffolds, or other culturing methods were excluded.

2.4 Data Extraction and Synthesis

Two reviewers pulled the articles from the databases and compiled them into a single list. Duplications were removed. After that, the titles and abstracts were evaluated, and irrelevant themes were excluded. If the abstract did not provide sufficient information, full texts were evaluated. Three reviewers then conducted a critical review of the selected papers (NA, RG, TH). When the reviewers disagreed, the issue was resolved by the editor, with another reviewer consulted if needed. Final decisions were made by the editor-in-chief, ensuring that the outcome reflected both scientific accuracy and fairness in the review process.

2.5 Studies Quality and Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies and the possibility of bias (9). Three domains were utilized to assess the study's quality (selection, comparability, and exposure). Each study was graded using a star system. The maximum number of stars awarded to the selection and exposure domains is four, while comparability is limited to two. Based on the overall NOS score, the studies were categorized as "Good," "Fair," or "Poor." Studies that received a score of 7 or more were regarded to be of high quality. The eight articles were evaluated using a modified version of the Critical Appraisal Skills Program (CASP) method.

Sections A, B, and C of the questions dealt with evaluating the introduction, methodology, and results & conclusion, respectively. The validity, outcomes, and application of the study were all evaluated in the critical assessment. For each study, the total level of evidence was assessed, and each study was given one of three grades: strong, moderate, or weak, respectively. A study that had a score of 67 percent or above was judged strong.

3. Results

3.1 Study Selection

A total of 507 records were identified through electronic database searching; one hundred fifty-four duplicate articles were excluded. The remaining three hundred and fifty-three articles were screened based on preset exclusion and inclusion criteria, and 298 were excluded. The remaining 55 articles were assessed for eligibility. After full text evaluation, 47 papers were excluded due to different reasons, like the use of immature teeth or using scaffolds with osteogenic potential or because authors were not mentioning the type of stem cells used in their studies. The final number of included studies in this review was only eight studies (Figure 1).

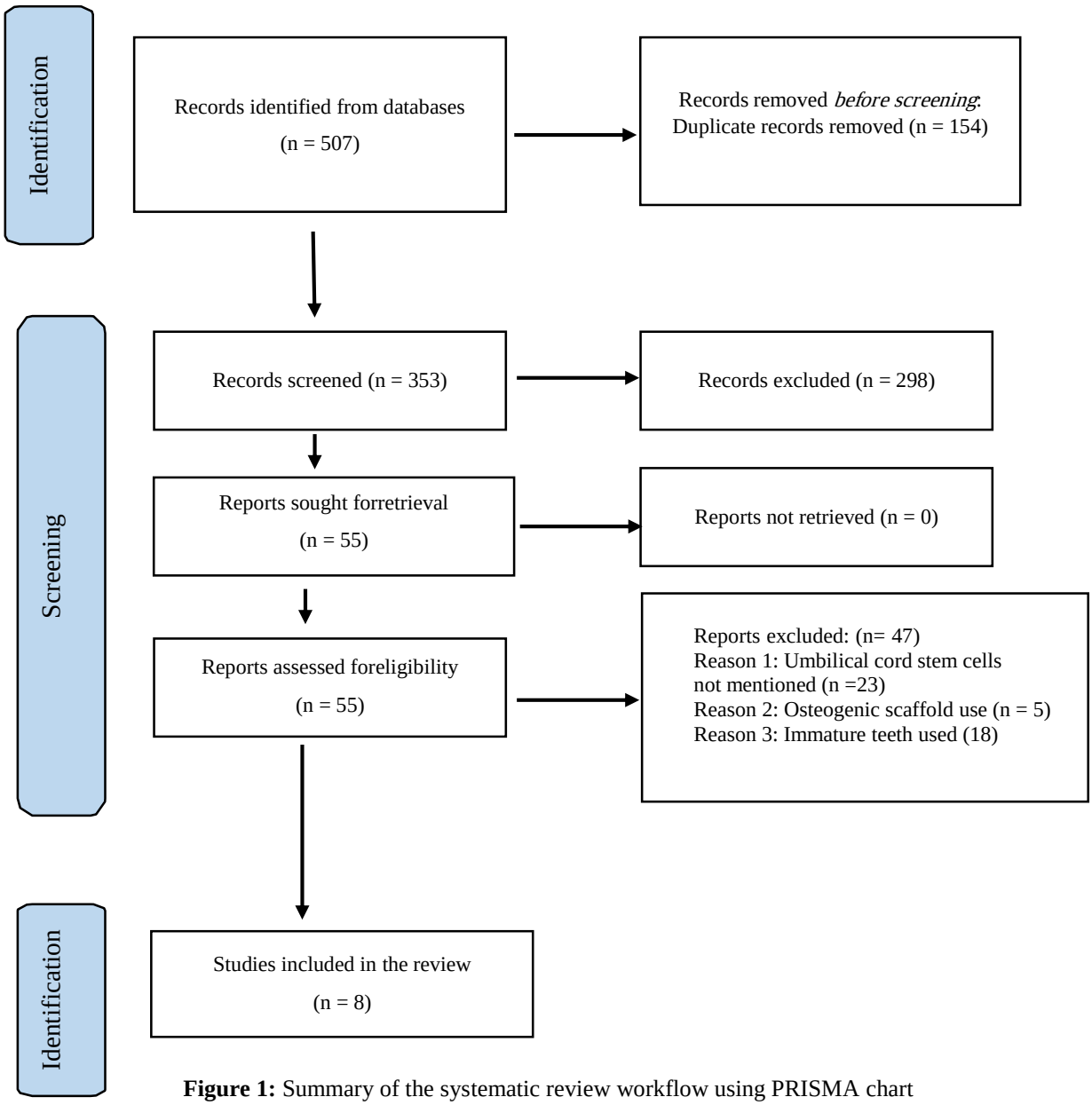

Figure 1: Summary of the systematic review workflow using PRISMA chart

3.2 Study Characteristics

Out of the 8 studies included, 7 studies were performed on animals; (1,2,10-14), while one study was performed on humans (4). Two studies used collagen type 1 scaffold (10,12), and one study used PPP (platelet poor plasma) scaffold (4), while the other 5 studies used the following scaffolds: human treated dentin matrix (1), Tooth germ cell conditioned medium (2), Pura Matrix (Peptide hydrogel scaffold) (11), Gelatin methacrylate (GelMA) hydrogel (13), or Metrigel hydrogel (14).

Five of the eight studies were performed in Asia (1,2,10-12), two in the USA (8,13), one in South America (4), and one in Tehran (14). Regarding the study design, four papers were case-control studies (1,2,10-13), while two studies were randomized controlled trials (4,14). Two studies were conducted *in vivo* (4,11), one study was conducted *in vitro* (2), while four studies included both, *in vivo* and *in vitro* (1,10,12,13).

3.3 Studies Quality Assessment and Risk of Bias

Based on the modified version of Critical Appraisal Skills Program (CASP) tool that was used for quality assessment, all eight papers were considered strong. Three of them scored (86.7%) (1,2,10), two scored (83.33%) (4,11), two scored (80%) (12,14), and one scored (73.33%) (Table 1).

Table 1: Study characteristics of the included studies

Authors	Scaffold	Study design	No. of Subjects	Main findings	Outcome	Statistical significance	Strength of study
Chen et al., 2015 (1)	hTDM ; TGC-CM	Case-control study	20 rats	huMCS can be induced into odontoblast-like cells by hTDM *in vivo*. hTDM-induced hUCMSCs expressed DSPP and DMP-1, whereas the uninduced hUCMSCs did not express these genes.	huMSC deposited dentin-like matrix when combined with hTDM *in vivo*	Differences in DSPP and DMP-1 expression between hTDM induced hUCMSCs and uninduced hUCMSCs were statistically significant. (P value <0.05)	86.7% - strong evidence
Li et al., 2013 (2)	Tooth germ cell conditioned medium	Cel-culture study	11 rats	hUCMSCs differentiate towards the odontogenic/osteogenic lineage by virtue of the TGC-CM-created microenvironment	TGC-CM-induced hUCMSCs had highalkaline phosphataseactivity and formed calcified nodules	The data indicated that the ALP activity of cells treated with TGC-CM was significantly higher than that of cells treated with regular medium at each time point (P<0.001)	86.7% -strong evidence
Brizuela et al., 2020 (4)	Platlet poor plasma	Randomized Controlled trial	36 humans	UC-MSCs encapsulated in a PP matrix used in this trial provided a different approach toregain vitality in mature teeth with the benefits of allogenic therapy.	The primary endpoints of the trial were the safety and efficacy of the PPPUC-MSC treatment. Efficacy at the first endpoint related to toothsurvival, the second endpoints included changes in cortical boneand pulpal response	Changes in lumen dimension during each time established a significant difference (Mann-Whitney test P = 0.0082) between the groups only in the reduction of the antero-posterior dimension between 6 and 12 monthsof follow-up.	86.7% - strong evidence

Zhang et al., 2020 (10)	Collagen 1	Case-control study	12 mice	Matrigel plug assay co-culturedhUCMSCs and V-hUCMSCs formed extensive vessel-like structures. - Both the hUCMSCs mono-culture and	Coculture groups showed pulp- like tissue regeneration. The cocultured group showed more extracellular matrix and vascularization than the mono-cultured group	There was a statistical significant between cell motility and adhesion ability of hUCMSCs treated with LE-TDM in comparison with hUSMSCs treated with regular media (P<0.001)	83.3% -strong evidence
Dissanayska et al., 2015 (11)	PuraMatrix (peptide hydrogel scaffold)	Case-control study	20 mice	Freshly isolated DPScs showed odonto/osteogenic, neurogenic, and adipogenic differentiation after being induced by induction media for 3 weeks. DPSc secrete pro-angiogenic growth factors which inhibits endothelial cell apoptosis.	The cocultured groups exhibited more extracellular matrix, vascularization, and mineralization than the DPSC-monocultures in vivo	The DPSCs displayed a significantly higher level of ALP activity than the DPSCs in monocultures (p,0.05)	83.3% - strong evidence
Zhang et al., 2020 (12)	Collage 1	Case-control study	12 mice	In vitro Matrigel angiogenesis assay and in vivo Matrigel plug assay indicated that co-cultured hUCMSCs and HUVECs promote vascular formationof HUVECs.	Study shows that coculture of hUCMSCs and HUVECs can promotevascular formation of HUVECs *in vitro* and *in vivo.* Co-transplantation of hUCMSCs and HUVECs can regenerate dental pulp-like tissue *in vivo*. Therefore, hUCMSCsand HUVECs may be used for rapid clinicaltranslation in the fieldof vascular	The proportion of living cells in HUVECs:hUCMSCs (5:1) group is higher than that of the hUCMSCs -alone group or HUVECs-alone group. With P value of <0.005	80% - strong evidence
Khayat et al., 2017 (13)	5% gelatin methacrylate (GelMA) hydrogel	Case-control study	15 rats	The results showed that GelMA-encapsulated hDPSC/HUVECs contributed to the formation of bioengineered pulp-like tissue that exhibited increased cellularity over *in vivo* implantation time. G1 root segments Exhibited cellularizedbioengineered pulp-like tissue after 13 d of *in vitro* culture	GelMA-encapsulated hDPSC/HUVECs contributed to the formation of organized and functional vasculature within highlycellularized pulp centers.It also exhibited cell attachment to the inner dentin surface, the formation of cellular extensions into dentin tubules of the human tooth root segment, and increased matrix deposition at the tooth root inner dentin layer. increased matrix deposition at the tooth root inner dentin layer.	NA	73.3% - strong evidence

Sabeti et al., 2024 (14)	Matrigel Hydrogel	Randomized Control trial	5 dogs	Regeneration of the pulp–dentin complex in immature permanent teeth with irreversible pulpitis is possible, and the best results were achieved when umbilical cord mesenchymal stem cells (UC-MSCs) were delivered with a matrigel hydrogel scaffold, provided that 2-4 mm of the apical pulp remains intact	UC-MSCs encapsulated in a Matrigel Hydrogel scaffold promoted regeneration of the pulp–dentin complex with normal pulp tissue, no inflammation, apical closure, and root wall thickening.	The use of umbilical cord mesenchymal stem cells (UC-MSCs) encapsulated in a matrigel hydrogel scaffold produced statistically significant improvements in apical closure, normal pulp regeneration, and reduction of inflammation compared to controls (P<.001).	80% strong evidence

Following reviewing the included studies, the NOS score varied between 4 and 9 (Table 2). Each study was assessed as excellent, with a score ranging from 7 to 9. The risk of bias was shown to be lowest in both the control definition within the selection domain and the ascertainment of exposure and response rate within the exposure domain, when the three domains were sub-divided.

Table 2: NOS scoring of the included studies

No.	Study authors	Selection				Comparability		Exposure			NOS score
1	Chen Y, et al., 2015 (1)	√	√	√	√	√	√	X	√	√	8
2	Li Tx, et al 2013 (2)	√	√	√	√	√	√	√	√	√	9
3	Brizuela C, et al., 2020 (4)	√	√	√	√	√	√	X	√	√	8
4	Zhang S, et al., 2020 (10)	√	√	√	√	√	√	√	√	√	9
5	Dissanayaka WL, et al., 2015 (11)	√	√	√	√	√	√	√	√	√	9
6	Zhang S, et al., 2020 (12)	√	√	√	√	√	√	X	X	√	8
7	Khayat A, et al., 2017 (13)	√	√	X	√	√	√	X	X	√	7
8	Sabeti, et al., (14)	√	√	√	√	√	√	√	√	√	9

3.4 Study Outcome

Regeneration of pulp using hUCMSCs was investigated on multiple scaffolds, such as platelet poor plasma, tooth germ cell conditioned medium, gelatin methacrylate hydrogel, collagen 1, and metrigel hydrogel scaffold, with an outcome of successful regeneration (1,2,4,10,11,12,14), The proportion of live cells in the human umbilical vein endothelial cells HUVECs:hUCMSCs (5:1) group is substantially greater than that in the hUCMSCs-alone or HUVECs-alone groups (p=0.05) (8,12). Chen et al. discovered that hUCMSCs had the capacity to develop into odontoblast-like cells when cultured in an odontogenic milieu including TGC-CM and human treated dentin matrix (hTDM) (1). Additionally, they discovered that when hUCMSCs were coupled with hTDM *in vivo*, they deposited a dentin-like matrix (1).

Li et al. established as proof-of-principle that hUCMSCs may develop into odontoblast-like cells when exposed to TGC-CM *in vitro* (2). Brizoila et al. discovered that UCMSCs encapsulated in a PPP matrix are safe, effective, and represent an innovative alternative treatment based on biological principles that promote dentin-pulp regeneration and periapical tissue

health in their triple blinded phase I and II RCT on 36 patients (4). Zhang et al. observed that hUCMSCs can develop into odontoblast-like cells in vitro when exposed to the microenvironment generated by the LE-TDM scaffold (10). Dissnayakka et al. shed light on the intricate intercellular signaling that occurs between HUVECs and DPSCs during angiogenesis and pulp regeneration. They discovered that DPSCs promoted the establishment of early vascular networks by enhancing HUVEC migration and raising VEGF expression. They concluded that both the DPSC-monoculture and coculture groups (DPSC: HUVECs in a 3:1 ratio) displayed vascularized pulp-like tissue with patches of osteo-dentin and the longer survival in mice following transplantation (11). Zhang et al. cocultured hUCMSCs and HUVECs and discovered that this approach promoted HUVEC vascular development. They advocated a 1:5 coculture ratio as the best coculture ratio (10). Zhang et al. postulated that angiogenesis occurs *via* stimulation of the HIF-1 signaling pathway by the long non-coding RNA HIF1A-AS2 (10). Khayat et al. demonstrated that GelMA hydrogels can support the formation of highly cellularized and vascularized hDPC/HUVEC-derived pulp-like tissue in *in vivo* implanted human root segments, facilitate cell attachment to the inner dentin surface of the tooth root, and promote the formation of cellular extensions into dentin tubules and the elaboration of reparative dentin matrix formation (13). Sabeiti et al. were able to regenerate the pulp-dentin complex *in vivo* with no inflammation when 2-4 mm of apical pulp tissue is left intact in immature teeth with irreversible pulpitis using UC-MSCs encapsulated in matrigel hydrogel scaffold (14).

4. Discussion

Pulpal tissue regeneration has been a crucial part to tackle regenerative endodontology by *in vitro* and *in vivo* studies. The central focus of this research is the ability to achieve successful pulpal regeneration (12). MSCs derived from Warton jelly have a strong proliferation ability. In the event of transplantation, they do not transform into teratogenic or cancerous cells (15). Umbilical cords, the source of WJMSCs, are readily available in great quantities without the use of intrusive harvesting techniques. Numerous investigations have established that WJMSCs can differentiate into odontoblast-like cells and depositing hard tissue (15). Notably, these cells are considered innocuous, since they are protected from viral infection by the placenta, which is beneficial for therapeutic purposes (1,16).

Through this systematic review, the ability of the umbilical cord mesenchymal stem cells (UC-MSCs) encapsulated in various bio scaffolds to regenerate the pulp dentin complex was assessed.

The most critical part of this review was the choice of the scaffold used to deliver the stem cells, because it has a direct impact on the outcome of the study and the regenerative power of the stem cells (17). The main purpose of the scaffold is to provide a suitable environment for cells' proliferation, differentiation, signaling, and adhesion, which will be important in the cell-cell and cell-matrix interactions (8,18). The designed scaffold must be non-toxic, biocompatible, and allow the regeneration of dental tissues. In the studies examined, PPP (Platelet Poor Plasma) was the primary scaffold utilized to demonstrate favorable pulpal regeneration; also, PPP clinical tests demonstrated 100 % success with the patient being asymptomatic during the 12-month follow-up period (19,20). Clinical examination indicated no pain to percussion or palpation; periodontal examination revealed no pockets greater than 3 mm in depth and normal physiological tooth movement (4,5). However, pulpal tissue regeneration has been recorded utilizing other scaffolds and cultures (13,14,16).

It was demonstrated that alginate hydrogels containing transforming growth factor (TGF)-beta have induced odontoblast-like cell differentiation and regulated dentine matrix secretion (16). Sabeiti et have reported that pulp-dentin complex was successfully regenerated using HUCMSCs encapsulated in a matrigel hydrogel scaffold with no inflammation when 2-4mm of apical pulp tissue was left intact in immature teeth with irreversible pulpitis (14), Additionally, it was determined that a hydrogel composed of gelatin methacrylate (GelMA) and human dental pulp stem cells (hDPSCs) and human umbilical vein endothelial cells (HUVECs) is a promising approach for pulpal revascularization in order to regenerate dental pulp tissues, as it demonstrated cell attachment to the inner dentine surface, cellular pulp, matrix and cell invasion into dentinal tubules (12,13).

Finally, Li et al. demonstrated that Tooth Germ Cell-Conditioned medium (TGC-CM) -induced hUCMSCs showed increased alkaline phosphatase activity and

produced calcified nodules, indicating that TGC-CM-induced hUCMSCs may develop into the odontogenic/osteogenic lineage as a result of the microenvironment established by TGC-CM (2).

Regarding the histological perspective of this systematic review, dentin-pulp complex regeneration means the regeneration of the neural, vascular, soft, and hard tissue of the pulp. If this outcome is achieved, then we would have a successful pulpal regeneration.

Some studies have different parameters to assess the outcome indicating the success or failure of treatment proposed (2,10,12). To begin, the study demonstrated that co-transplantation of human umbilical cord mesenchymal stem cells and human umbilical vein endothelial cells HUVECs can result in HUVECs angiogenesis *via* noncoding RNA HIF1A-AS2-mediated activation of the HIF-1 signaling pathway at a ratio of 1:5. (hUCMSCs: HUVECs) (12).

Additionally, hUCMSCs demonstrated functional endothelial indicators (CD31, e NOs, vWF), odontoblast markers (DSPP, DMP-1, DSP), and the development of vessel-like structures when treated with liquid extract of human treated dentin matrix (LE-TDM) and vascular endothelial growth factor (VEGF) (10). Additionally, one study suggested that generated hUCMSCs might develop into odontogenic/osteogenic cells due to their high alkaline phosphatase (ALP) activity and production of calcified nodules (2).

Under the right conditions and medium used, the cells from the umbilical cord can differentiate into osteoblasts, adipocytes, and neural-like cells (21,22). As such, with various outcomes of the studies, hUCMSC can be successfully used in pulpal regeneration to serve as the future of endodontics. As a proof-of-concept, hUCMSCs exhibit multi-potency and can differentiate into odontoblast-like cells when cultured with TGC-CM (2). Additionally, encapsulated UC-MSCs in a PPP matrix demonstrated no side effects and constituted a novel alternative treatment based on biological principles that promotes dentin-pulp regeneration and periapical tissue health (4). Furthermore, hUCMSCs may be exploited for quick clinical translation in the field of vascular regeneration for the treatment of endothelial dysfunction as well as dental pulp tissue engineering (12).

The choice of experimental subjects was not uniform among the studies. Some were performed on rats (1,2,10-13), one on dogs (14), and one on humans (4). Also, randomization has been done only in one study (4). As such, the remaining studies did not address potential sources of bias. Not all the studies have clear inclusion and exclusion criteria as in papers (4,11,12). On the other hand, three studies (2,10,13) have mentioned both inclusion and exclusion criteria, while one study (1) have only mentioned an inclusion criterion. Further, not all studies had statistical analyses (2,5,13), which is considered a major weakness. Another limitation found is that various studies had the issue of not having the proper scaffold to allow pulpal regeneration (10,12). According to these studies, collagen type I was shown to be biocompatible with VEGF-induced hUCMSCs (V-hUCMSCs; V), but lacked the potential to generate angiogenesis, resulting in no contact between the cells and dentinal wall owing to collagen I scaffold shrinking. (10,12). Also, some of the studies had low numbers of subjects and a short follow-up, which might alter the efficacy of the results (12,14).

While UC-MSCs offer many strengths, their performance may lag in certain lineage differentiations or under some environmental constraints compared to other MSC sources.

Dental MSCs (especially stem cells from human exfoliated decidous teeth (SHED), dental pulp-derived MSCs) may serve as strong alternate or complementary sources, especially when odontoblastic differentiation is a major goal; but issues of donor variability and lower yields need to be managed (23).

5. Conclusions

Human umbilical cord stem cell transplantation appears to upgrade pulpal regeneration and recovery in both humans and animals; however, these discoveries are based on diverse models and various interventions and control with a risk of bias.

Different studies have shown pulpal tissue regeneration using other scaffolds and cultures, but they were not extremely effective. Taking the results into consideration, UC-MSCs encapsulated in a PPP matrix and matrigel hydrogel scaffolds are a safe and effective alternative treatment based on biological principles that promote dentin-pulp regeneration and periapical tissue health.

Further randomized clinical trial studies are required to determine whether regeneration of the entire tooth including periodontal ligament, dentin, enamel, and

cementum is possible using hUCMSCs.

Conflict of Interests

The authors declare no conflict of interests related to the preparation or publication of this systematic review.

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