Stem Cells Harvested From Exfoliated Deciduous Teeth - A Review

Type of manuscript: Review Article

KiranSrinivasB[1],Gifrina Jayaraj[2],YuvarajBabu K[3]

[1]Saveetha Dental College and Hospitals, Saveetha institute of Medical and TechnicalSciences,Saveetha University, Chennai
[2]Reader , Department of Oral Pathology ,Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences,SaveethaUniversity,Chennai

[3]Assistant Professor, Department of Anatomy, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai

Email ID:
[1]151901072.sdc@saveetha.com,[2]gifrina@saveetha.com,[3]yuvarajbabu@saveetha.com

Abstract: Stem cells harvested from exfoliated deciduous teeth are a type of mesenchymal cells, serving its main purpose for regenerative treatment. They have lots of clinical applications. They are studied for their distinct proliferative properties. It helps in regeneration of tissues in the site of an injury and also helps in reducing the healing time of an injury. It also serves as the research interest for many because of its easy source of availability, extensive regenerative capacity and multiple lineage properties. This article is in the narrative format of previous research articles on stem cells exfoliated from deciduous teeth, which discusses various complex procedures associated with SHED - like extraction, isolation, post extraction and banking of it mentioned from other articles as well. SHED has a lot of branches to be studied and understood deeply. So that they can be implemented for many human uses. It is used for future as well as diagnosis.

Keywords: Derived stem cells, Exfoliated deciduous tooth, extraction, mesenchymal stem cells, proliferation, regeneration.

1. INTRODUCTION

"Differentiation" biologically is considered to be a special property where already existing cells modify themselves into new cells to perform a varied specific function(Xuet al., 2020). These differentiation properties are well performed by the stem cells, derived from various places like blood, amniotic fluid, mesenchymalcells(Escobar and Chaparro, 2016). These stem cells are now used in different ways like - the replacement of lost cells and tissues, regeneration of lost organs. Pluripotent stem cells possess the capability ofself renewing and can develop into germ layers(Cronwright et al., 2005). Stem cells extracted during the embryonic stage are called embryonic stem cells and if extracted from the adults it is called as adult stem cells (Han et al., 2020). Stem cells harvested from exfoliated deciduous teeth are a type of Mesenchymal stem cells (MSCs), studied for their regenerative potential. Stem cells harvested from exfoliated deciduous teeth(Harrita and Santhanam, 2019) [SHED] were first identified by Miura et al in 2003(Miura et al., 2003). SHED are heterogeneous groups of population isolated from dental pulpal tissues, remaining in exfoliated

deciduousteeth(Abithaand Santhanam, 2019; Sukumaran and Padavala, 2018), and SHED tends to be the peak of most research works because of its high regeneration capacity, and other related aspects(Chadipiralla et al., 2010). SHED exhibits higher osteogenic differentiation potency when compared to human dental pulpal cells.(Sukarawan et al., 2014) Every child loses its tooth, so SHED is easily available, without much complications. Most of the regenerative sectors of SHED remains to be a mystery. Cryopreservation is also associated with SHED in banking. It helps in offering SHED for therapeutic and regenerative applications(Arora et al., 2009).

As SHED remained to be a high field of interest for many entrepreneurs, many previous studies are done on its various capacities like proliferation, differentiation and maturation(Rattanawarawipa et al., 2016). Most of the research articles are based on its comparison of properties with other stem cells with the properties like regeneration, proliferation and stability during the usage of these cells in advanced fields(Van Pham, 2017). The methods of isolation include dissolving with solvents and other forms of immiscible liquids. Their efficiency in regeneration and immunotherapy were discussed in other cases(George, 2015). Markers for marking stem cells using various markers along with the classes of the markers which they belong to were also assayed along with it(Chai, 2013). Advantage of using dental based stem cells were categorised - non immunogenic property, serving as a good match for the entire family, risk of communicable diseases and specific non-communicable diseases could be avoided. Isolation guidelines, sample selection criteria were analysed and were the regions that were covered.(Bakopoulou et al., 2011)

The present research has origins from the team of investigators where previous studies were done based on clinical reports(Gunasekaran and Abilasha, 2016; Palati et al., 2020; Prasanna and Gheena, 2016; Shree et al., 2019), interventional studies(Ahad and Gheena, 2016; Hannah et al., 2018; Krishnan et al., 2018; Manohar and Abilasha, 2019), in vitro studies(Palati et al., 2019; Sarbeen et al., 2016; Sheriff et al., 2018; Uma et al., 2018)The main aim of this article is to review and analyse various advancements and techniques associated with it. Every article obtained is analysed in detail and in a comparative manner. Procedures in SHED such as isolation, extraction,banking are reviewed in a systematic manner from other articles.

2. METHODOLOGY

This article speaks about different approaches on SHED from various previous research articles in a narrative manner. This systematic review is done based on various kinds and numbers of articles obtained from platforms such as pubmed, pubmedcentral and google scholar. These articles were collected with a restriction in the timeline of 2003-2020. The articles were selected based on inclusion and exclusion criteria. Inclusion criteria of articles are the original research papers, in vitro studies in various clinical conditions and articles that contain suitable pros and cons. Some articles are excluded if they are reviewed or retracted articles. They were also rejected if the articles were from other languages. All the articles were selected based on various methodologies and techniques associated with SHED, determined with the help of article title and abstract.

When article holding websites like pubmed, pubmed central and google scholar were analysed for SHED more than 60 articles were found. When the articles were categorised for under suitable inclusion as well as exclusion criteria only 32 articles were found. This study is done systematically from the obtained full text articles and the quality of articles used was assessed using a quality assessment tool and graded as strong, moderate and weak. The level

of evidence of the reviewed articles were categorized as per the criteria of the centre for evidence-Based medicine, Oxford, UK(Howick et al., 2011).

What Are Stem Cells?

Stem cells are specialised types of cells that can differentiate themselves to form and develop into different types of cells they can be used to replace lost and degenerated cells(Richards, 2004). The property of supreme regeneracy makes them special(Erler et al., 2017). Stem cell therapy involves usage of these stem cells for biological regeneration as well as generation of lost tissues, and to heal them completely. Stem cells are usually extracted from various sites of the human body(Hampton, 2007).

Type Of Stem Cells Are Harvested From Exfoliated Deciduous Teeth

Stem cells harvested from the exfoliated deciduous teeth [SHED] is one of the main types of dental stem cells(Yang et al., 2019). It is a type of mesenchymal stem cells (Wang et al., 2020). They are widely used in the regenerative fields as they possess properties like pluripotency, so that it can generate germ layers and tissues. They are also termed as high quality postnatal cells that are highly proliferative in nature(Al-Dalahmah et al., 2020).

Isolation Of SHED

SHED are normally derived from children between the ages of 6 and 8 years of old(Park et al., 2016). Children of these ages are monitored and deciduous teeth are collected from them as the tooth SHED off. In some rare case scenarios the subjected children may not shed a tooth within the specific time [eruption delay], prophylaxis was used as an antibiotic(Kantrong et al., 2020), in such cases the tooth is obtained from other subjects who fall in the same age category. After obtaining the tooth, they are isolated with the help of collagenase type 1, digestion of various proteins is achieved through the enzyme then the method of single cell suspension is followed to obtain SHED(Ariffin et al., 2016).

Banking Of SHED

After the stem cells are obtained, the stem cells undergo the process of banking by which stem cells are stored as well as preserved(Kurtzberg, 2017). Most common type of preservation is cryopreservation, where the cells are stored in - 196^{o}C(Doğan et al., 2012). Banking of tooth cells are done for future usage of and many advantageous processes. Helps in treating many diseases at its earlier stages(Naji et al., 2017).

Role of Various Growth Factors InSignalling

(i) Fibroblast factor: Basic fibroblast growth factor plays an important role in the inhibition of SHED when the proliferation of SHED occurs osteogenically(Sluzalska et al., 2020)

(ii) **β**-Canteninsignalling:It plays a major role in the activation of proliferation capacity of the deciduous derived stem cells. It regulates its proliferation.

(iii) Notch signalling: This type of signalling controls various functions of stem cells. Involving various kinds of cell specific differentiation factors(Chen et al., 2017).

Potential Application Of SHED

SHED is distinct for its high plasticity and cross lineage property, through which it is able to regenerate so easily(Glauche et al., 2007). The expression of odontoblastic differentiation is also done as an applied field in the regenerative aspects.

Guidelines Involved In Extraction Of Tooth Harvesting

The pulp should be in red colour when the deciduous tooth sheds off, to show the time of shedding. Dead stem cells cannot be used for any of the purposes. They should be extracted with the two-third roots because if the tooth is with less pulp it is more advantageous(Liu et al., 2020).

Post-extraction Control

After collection and dissolution the collected sample is gently washed with 70% ethanol. Buffer is added along with the saline. Provision of nourishment is done by proper nourishing medium. This technique is also called cryogenics(Mokrý et al., 2004) After nourishment the SHED is properly sealed with the wax. It is kept under -196^{o}C after preserving it in the room temperature for 48 hours(Zang et al., 2019) it is kept and maintained using a sterile barbed broach(Mohan et al., 2011).

Applications

SHED expressed as a result of surface markers with dissolved enzymes has more proliferation rates than other stem cells. It has greater odontogenic capacity than all other stem cells derived from the mesenchyme. It is easily available when compared to other stem cells like cells obtained from the bone marrow(Yurtsever et al., 2020). It shows less morbidity than other stem cells. SHED has the highest proliferative capacities. So they can recover lost tissues from parts of the body like bone and cartilage. Research is undergoing now to graft adipose tissue as well as elastic cartilages from the stem cells exfoliated from deciduous teeth(Nourbakhsh et al., 2011)

3. RESULTS AND DISCUSSION

The key research findings of the reviewed literature is listed in table 1. From the few articles obtained, it is clear that the tooth is extracted mostly from seven year old children, as rates of proliferation are highest during that time period(Park et al., 2016). Collagenase 1 is the most preferred enzyme for isolation, it has the ability to dissolve most of the organic components of the deciduous tooth(Kantrong et al., 2020). Prophylaxis is used as an antibiotic to prevent growth of any pathogen on the cells during extraction(Ariffin et al., 2016). Universally accepted post extraction is the usage of sterile barbed broach during the preservation of SHED. The main advantage of using it is that it causes no injuries to the pulpal region . Sorting cell suspension is also a famous procedure done during isolation of SHED(Ariffin et al., 2016). Cryopreservation in the banking of SHED is effective when it is stored in cryo after 48 hours of storing in the normal room temperature(Mohan et al., 2011).

The involvement of exponential growth curves were essential in finding different rates such as rates of proliferation and differentiation. But it was not implemented in the studies, which could be more accurate if the rates are calculated(De Haan et al., 2017). Its other uses are yet to be analysed.

Wide ranged studies are required in case of SHED. 100% regeneration capacity is not outcasted so it is difficult to find out its usage in other fields. Limited amount of articles about immunogenic properties and extraction techniques.

Methods of extraction, isolation techniques should be analysed so that sophisticated ways of isolation can be found. If 100% regeneration capacities are found, full organ restoration can be achieved. More articles should be analysed for other usages of SHED too.

4. CONCLUSION

SHED always has multiple applications with limitations. Major difficulties associated with SHED is its identification and purification. Many fields of it are still under discussion. All possible outcomes help mankind in many ways. Awareness about various qualities of SHED should be given to all so that they can know about its various cure to many diseases.

CONFLICT OF INTEREST

The author declares that there was no conflict of interest in the present study.

AUTHOR CONTRIBUTION

KiranSrinivas B - Literature search, data collection, analysis and manuscript writing.
GifrinaJayaraj - Data verification, manuscript drafting.
YuvarajBabu K - Data verification, manuscript drafting.

5. REFERENCES

[1] Abitha T and Santhanam A (2019) Correlation between bizygomatic and maxillary central incisor width for gender identification. *Brazilian Dental Science*. DOI: 10.14295/bds.2019.v22i4.1775.

[2] Ahad M and Gheena S (2016) Awareness, attitude and knowledge about evidence based dentistry among the dental practitioner in Chennai city. *Research Journal of Pharmacy and Technology* 9(11). A & V Publications: 1863–1866. Available at: http://www.indianjournals.com/ijor.aspx?target=ijor:rjpt&volume=9&issue=11&article=009.

[3] Al-Dalahmah O, Nicholson J, Draijer S,et al. (2020) Galectin-3 diminishes Wnt signaling in the postnatal subventricular zone. *Stem cells*. DOI: 10.1002/stem.3202.

[4] Ariffin SHZ, Manogaran T, Abidin IZZ, et al. (2016) Isolation and morphology of Stem Cells from Deciduous Tooth (SHED) and Human Dental Pulp Stem Cells (hDPSC). DOI: 10.1063/1.4966718.

[5] Arora V, Arora P and Munshi AK (2009) Banking Stem Cells from Human Exfoliated Deciduous Teeth (SHED): Saving for the Future. *Journal of Clinical Pediatric Dentistry*. DOI: 10.17796/jcpd.33.4.y887672r0j703654.

[6] Bakopoulou A, Leyhausen G, Volk J, et al. (2011) Assessment of the impact of two different isolation methods on the osteo/odontogenic differentiation potential of human dental stem cells derived from deciduous teeth. *Calcified tissue international* 88(2): 130–141. DOI: 10.1007/s00223-010-9438-0.

[7] Chadipiralla K, Yochim JM, Bahuleyan B, et al. (2010) Osteogenic differentiation of stem cells derived from human periodontal ligaments and pulp of human exfoliated deciduous teeth. *Cell and tissue research* 340(2). Springer: 323–333. DOI: 10.1007/s00441-010-0953-0.

[8] Chai J (2013) Validity of Markers for Epithelial Cells and Mesenchymal Cells. *Stem Cells and Cancer Stem Cells, Volume 10*. DOI: 10.1007/978-94-007-6262-6_3.

[9] Chen X, Li S, Zeng Z, et al. (2017) Notch1 signalling inhibits apoptosis of human

dental follicle stem cells via both the cytoplasmic mitochondrial pathway and nuclear transcription regulation. *The international journal of biochemistry & cell biology* 82: 18–27. DOI: 10.1016/j.biocel.2016.11.013.

[10] Cronwright G, Le Blanc K, Götherström C, et al. (2005) Cancer/testis antigen expression in human mesenchymal stem cells: down-regulation of SSX impairs cell migration and matrix metalloproteinase 2 expression. *Cancer research* 65(6): 2207–2215. DOI: 10.1158/0008-5472.CAN-04-1882.

[11] De Haan JJ, Haitjema S, den Ruijter HM, et al. (2017) Growth Differentiation Factor 15 Is Associated With Major Amputation and Mortality in Patients With Peripheral Artery Disease. *Journal of the American Heart Association* 6(9). DOI: 10.1161/JAHA.117.006225.

[12] Doğan A, Yalvaç ME, Rizvanov A, et al. (2012) Effect of F68 on cryopreservation of mesenchymal stem cells derived from human tooth germ. *New Biotechnology*. DOI: 10.1016/j.nbt.2012.08.038.

[13] Erler P, Sweeney A and Monaghan JR (2017) Regulation of Injury-Induced Ovarian Regeneration by Activation of Oogonial Stem Cells. *STEM CELLS*. DOI: 10.1002/stem.2504.

[14] Escobar CH and Chaparro O (2016) Xeno-Free Extraction, Culture, and Cryopreservation of Human Adipose-Derived Mesenchymal Stem Cells. *STEM CELLS Translational Medicine*. DOI: 10.5966/sctm.2015-0094.

[15] George T (2015) The Scope of Stem Cells in Periodontal Regeneration. *Journal of Dentistry, Oral Disorders & Therapy*. DOI: 10.15226/jdodt.2015.00139.

[16] Glauche I, Cross M, Loeffler M, et al. (2007) Lineage Specification of Hematopoietic Stem Cells: Mathematical Modeling and Biological Implications. *Stem Cells*. DOI: 10.1634/stemcells.2007-0025.

[17] Gunasekaran G and Abilasha R (2016) TOOTH SENSITIVITY AMONG RESIDENTIAL UNIVERSITY STUDENTS IN CHENNAI. *Asian Journal of Pharmaceutical and Clinical Research*. DOI: 10.22159/ajpcr.2016.v9s2.13228.

[18] Hampton T (2007) Stem Cells Obtained From Amniotic Fluid. *JAMA*. DOI: 10.1001/jama.297.8.795.

[19] Hannah R, Ramani P, Herald. J. Sherlin, et al. (2018) Awareness about the use, Ethics and Scope of Dental Photography among Undergraduate Dental Students Dentist Behind the lens. *Research Journal of Pharmacy and Technology*. DOI: 10.5958/0974-360x.2018.00189.0.

[20] Han NR, Baek S, Kim H-Y, et al. (2020) Generation of embryonic stem cells derived from the inner cell mass of blastocysts of outbred ICR mice. *Animal cells and systems* 24(2): 91–98. DOI: 10.1080/19768354.2020.1752306.

[21] Harrita S and Santhanam A (2019) Determination of Physical Height Using Clinical Crown Height of Deciduous Teeth. *Indian Journal of Forensic Medicine & Toxicology*. DOI: 10.5958/0973-9130.2019.00255.x.

[22] Howick J, Chalmers I, Glasziou P, et al. (2011) The 2011 Oxford CEBM evidence levels of evidence (introductory document). *Oxford Center for Evidence Based Medicine*.

[23] Kantrong N, Mongkontunpimon W, Supameteeworakul S, et al. (2020) Differential induction of surface chemical compositional change on tooth structure by glass ionomer restorative materials. *Odontology / the Society of the Nippon Dental University*. DOI: 10.1007/s10266-020-00528-6.

[24] Krishnan RP, Ramani P, Sherlin HJ, et al. (2018) Surgical Specimen Handover from Operation Theater to Laboratory: A Survey. *Annals of maxillofacial surgery* 8(2): 234–238. DOI: 10.4103/ams.ams_51_18.

[25] Kurtzberg J (2017) A History of Cord Blood Banking and Transplantation. *STEM*

CELLS Translational Medicine. DOI: 10.1002/sctm.17-0075.

[26] Liu BY, Liu J, Zhang D, et al. (2020) Effect of silver diammine fluoride on micro-ecology of plaque from extensive caries of deciduous teeth - in vitro study. *BMC oral health* 20(1): 151. DOI: 10.1186/s12903-020-01141-3.

[27] Manohar J and Abilasha R (2019) A Study on the Knowledge of Causes and Prevalance of Pigmentation of Gingiva among Dental Students. *Indian Journal of Public Health Research & Development*. DOI: 10.5958/0976-5506.2019.01859.x.

[28] Miura M, Gronthos S, Zhao M, et al. (2003) SHED: stem cells from human exfoliated deciduous teeth. *Proceedings of the National Academy of Sciences of the United States of America* 100(10). National Acad Sciences: 5807–5812. DOI: 10.1073/pnas.0937635100.

[29] Mohan R, Benjamin M, Rao S, et al. (2011) Accidental ingestion of a barbed wire broach and its endoscopic retrieval: Prevention better than cure. *Indian Journal of Dental Research*. DOI: 10.4103/0970-9290.94681.

[30] Mokrý J, Cízková D, Filip S, et al. (2004) Nestin expression by newly formed human blood vessels. *Stem cells and development* 13(6): 658–664. DOI: 10.1089/scd.2004.13.658.

[31] Naji A, Suganuma N, Espagnolle N, et al. (2017) Rationale for Determining the Functional Potency of Mesenchymal Stem Cells in Preventing Regulated Cell Death for Therapeutic Use. *STEM CELLS Translational Medicine*. DOI: 10.5966/sctm.2016-0289.

[32] Nourbakhsh N, Soleimani M, Taghipour Z, et al. (2011) Induced in vitro differentiation of neural-like cells from human exfoliated deciduous teeth-derived stem cells. *The International journal of developmental biology* 55(2): 189–195. DOI: 10.1387/ijdb.103090nn.

[33] Palati S, Ramani P, Herald. J. Sherlin, et al. (2019) Age Estimation of an Individual Using Olze's Method in Indian Population-A Cross-Sectional Study. *Indian Journal of Forensic Medicine & Toxicology*. DOI: 10.5958/0973-9130.2019.00179.8.

[34] Palati S, Ramani P, Shrelin H, et al. (2020) Knowledge, Attitude and practice survey on the perspective of oral lesions and dental health in geriatric patients residing in old age homes. *Indian Journal of Dental Research*. DOI: 10.4103/ijdr.ijdr_195_18.

[35] Park Y-J, Cha S and Park Y-S (2016) Regenerative Applications Using Tooth Derived Stem Cells in Other Than Tooth Regeneration: A Literature Review. *Stem Cells International*. DOI: 10.1155/2016/9305986.

[36] Prasanna GE and Gheena S (2016) A study of empathy across students from 4 health disciplines among 1st years and Final years. *Research Journal of Pharmacy and Technology*. DOI: 10.5958/0974-360x.2016.00286.9.

[37] Rattanawarawipa P, Pavasant P, Osathanon T, et al. (2016) Effect of lithium chloride on cell proliferation and osteogenic differentiation in stem cells from human exfoliated deciduous teeth. *Tissue and Cell*. DOI: 10.1016/j.tice.2016.08.005.

[38] Richards M (2004) The Transcriptome Profile of Human Embryonic Stem Cells as Defined by SAGE. *Stem Cells*. DOI: 10.1634/stemcells.22-1-51.

[39] Sarbeen JI, InsiraSarbeen J and Gheena S (2016) Microbial variation in climatic change and its effect on human health. *Research Journal of Pharmacy and Technology*. DOI: 10.5958/0974-360x.2016.00359.0.

[40] Sheriff KAH, Ahmed Hilal Sheriff K and Santhanam A (2018) Knowledge and Awareness towards Oral Biopsy among Students of Saveetha Dental College. *Research Journal of Pharmacy and Technology*. DOI: 10.5958/0974-360x.2018.00101.4.

[41] Shree KH, Hema Shree K, Ramani P, et al. (2019) Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma – a Systematic Review with Meta Analysis. *Pathology & Oncology Research*. DOI: 10.1007/s12253-019-00588-2.

[42] Sluzalska KD, Slawski J, Sochacka M, et al. (2020) Intracellular partners of fibroblast growth factors 1 and 2 - implications for functions. *Cytokine & growth factor reviews*. DOI: 10.1016/j.cytogfr.2020.05.004.
[43] Sukarawan W, Nowwarote N, Kerdpon P, et al. (2014) Effect of basic fibroblast growth factor on pluripotent marker expression and colony forming unit capacity of stem cells isolated from human exfoliated deciduous teeth. *Odontology / the Society of the Nippon Dental University* 102(2). Springer: 160–166. DOI: 10.1007/s10266-013-0124-3.
[44] Sukumaran G and Padavala S (2018) Molar incisor hypomineralization and its prevalence. *Contemporary Clinical Dentistry*. DOI: 10.4103/ccd.ccd_161_18.
[45] Uma PK, Ramani P, Sherlin H, et al. (2018) Diet and exercise among students of a wellreputed dental college in Chennai: A questionnaire-based survey. *International Journal of Orofacial Biology*. DOI: 10.4103/ijofb.ijofb_1_19.
[46] Van Pham P (2017) *Mesenchymal Stem Cells: Isolation, Characterization and Applications*. BoD – Books on Demand. Available at: https://play.google.com/store/books/details?id=Z22PDwAAQBAJ.
[47] Wang L, Yu C, Chang T, et al. (2020) In situ repair abilities of human umbilical cord-derived mesenchymal stem cells and autocrosslinked hyaluronic acid gel complex in rhesus monkeys with intrauterine adhesion. *Science advances* 6(21): eaba6357. DOI: 10.1126/sciadv.aba6357.
[48] Xu D, Wan Y, Li Z, et al. (2020) Tailorable hierarchical structures of biomimetic hydroxyapatite micro/nano particles promoting endocytosis and osteogenic differentiation of stem cells. *Biomaterials science*. DOI: 10.1039/d0bm00443j.
[49] Yang X, Ma Y, Guo W, et al. (2019) Stem cells from human exfoliated deciduous teeth as an alternative cell source in bio-root regeneration. *Theranostics* 9(9): 2694–2711. DOI: 10.7150/thno.31801.
[50] Yurtsever MÇ, Kiremitci A and Gümüşderelioğlu M (2020) Dopaminergic induction of human dental pulp stem cells by photobiomodulation: comparison of 660nm laser light and polychromatic light in the nir. *Journal of photochemistry and photobiology. B, Biology* 204: 111742. DOI: 10.1016/j.jphotobiol.2019.111742.
[51] Zang X, He L, Zhao L, et al. (2019) Adipose-derived stem cells prevent the onset of bisphosphonate-related osteonecrosis of the jaw through transforming growth factor β-1-mediated gingival wound healing. *Stem cell research & therapy* 10(1): 169. DOI: 10.1186/s13287-019-1277-y.

Table 1 - Description Of Included Studies

Sl.No	**Author Name**	**Year**	**Type Of Study**	**Sample Size**	**Key Findings**	**Level Of Incidence**
1	Miura M (Miura et al., 2003)	2003	Randomised controlled trial	49	First extracted SHED in 2003 from the deciduous tooth of a child aged 6.	1
2	Richards (Richards, 2004)	2004	Expert opinion	-	Depicted regeneration capacity of stem cells by time conspiracy method.	5

					The rate at which they could proliferate.	
3	Mokry(Mokrý et al., 2004)	2004	Case controlled study	18	Successfully regenerated blood vessels, with the help of niche - the stem cells that are extracted from the marrow.	3
4	Hampton T (Hampton, 2007)	2007	Expert opinion	-	Stem cell therapy with the help of mesenchymal stem cells.	5
5	Cronwright(Cronwright et al., 2005)	2007	Expert opinion	-	Efficiency of metalloproteinase 2 in mesenchymal stem cell expression.	5
6	Glauche(Glauche et al., 2007)	2007	Expert opinion		Lineage specification of hematopoietic stem cells using mathematical modelling and biological implications.	5
7	Arora V (Arora et al., 2009)	2009	Expert opinion	-	Found that SHED could be stored and can be used for future use with the help of preservable mediums.	5
8	Chadipiralla(Chadipiralla et al., 2010)	2010	Case series	-	Osteogenic differentiation of stem cells derived from human periodontal ligament and pulp of exfoliated tooth, by tissue - cell	4
9	Nourbakhsh(Nourbakhsh et al., 2011)	2011	Randomised controlled trial	72	Induced in vitro differentiation of neural like cells from human exfoliated deciduous teeth derived cells.	1
10	Dogan A	2012	Case controlled	12	Effect of F68 in	3

	(Doğan et al., 2012)		study		cryopreservation of mesenchymal stem cells, derived from human tooth germ.	
11	Chai J (Chai, 2013)	2013	Case controlled study	44	Expressed the validity of markers for the epithelial as well as mesenchymal stem cells.	3
12	Sukarawan(Sukarawan et al., 2014)	2014	Case controlled study	30	Analysed the effects of fibroblast growth factor	1
13	George T (George, 2015)	2015	Expert opinion	-	Detected the scope of stem cells in periodontal regeneration using meta-cellular analysis.	3
14	Park Y (Park et al., 2016)	2016	Expert opinion	-	Regeneration of degenerated cells in dental stem cells using dental scheme.	4
15	Ariffin(Ariffin et al., 2016)	2016	Expert opinion	-	Stem cell therapy induced in deciduous tooth	5
16	Escobar (Escobar and Chaparro, 2016)	2016	Case controlled study	47	Extraction, culture and cryopreservation of Human adipose derived mesenchymal stem cells	1
17	Rattanawarawipa(Rattanawarawipa et al., 2016)	2016	Case series	23	Analysis of cell proliferation and cell differentiation in stem cell	5
18	Kurtzberg(Kurtzberg, 2017)	2017	Expert opinion	-	Cord blood banking and transplantation by glu 1 mechanism.	3
19	Naji A (Naji et al., 2017)	2017	Case series	66	Analysis of determining the functional potency of the mesenchymal stem cells.	1

20	Sluzalska(Sluzalska et al., 2020)	2017	Randomised controlled trial	45	Eruption delay and its management in children aged between 6 to 8.	5
21	Chen X (Chen et al., 2017)	2017	Expert opinion	-	Dissolving organic calcium with the help of collagenase 1 dissolving medium.	5
22	Van Pham (Van Pham, 2017)	2017	Case series	32	Isolation and banking methods using magnification and characterisation of application.	5
23	Erler P (Erler et al., 2017)	2017	Case controlled study	12	Regulation of injury induced ovarian regeneration by activation of oogonial stem cells.	5
24	Yang X (Yang et al., 2019)	2019	Case controlled study	47	Alternative cell source for extraction of SHED.	3
25	Zang X (Zang et al., 2019)	2019	Expert opinion	-	Studied jaw formation related osteonecrosis by mediated factor.	5
26	Xu D (Xu et al., 2020)	2020	Expert opinion	-	Studied structure of endocytosis derived differentiation of stem cells.	5
27	Wang L (Wang et al., 2020)	2020	Case series	23	Observed in situ reparative changes of SHED in tooth repair.	4
28	Bakopoulou(Bakopoulou et al., 2011)	2020	Expert opinion	-	Analysis of various types of signalling in the postnatal subventricular zone.	5
29	Kantrong(Kantrong et al., 2020)	2020	Randomised controlled trial	45	Differential induction of surface and chemical compositional change on the tooth surface.	1

30	Liu B Y (Liu et al., 2020)	2020	Case controlled study	45	Analysis about the depth of caries and using stem cells using microecology of plaque.	3
31	Yurtsever(Yurtsever et al., 2020)	2020	Randomised controlled trial	28	Induction of human dental stem cells by photo - biomagnification.	1
32	Han NR (Han et al., 2020)	2020	Expert opinion	-	Generation of embryonic stem cells derived from the inner cell mass.	5