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Original Article

Ameliorative potential of stem cells from human exfoliated deciduous teeth (SHED) in preclinical studies: A meta-analysis

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ABSTRACT

The preclinical and clinical role of mesenchymal stem cells from various adult sources is extensively investigated and established in regenerative medicine. However, the comprehensive exploration of the therapeutic potential of Stem cells from human exfoliated deciduous teeth (SHED) is inadequate. Therefore, we performed a systematic meta-analysis of preclinical animal model studies in several diseases to provide insight into SHED's efficacy and therapeutic potential. Two blinded and independent investigators searched the available online databases and scrutinized the included studies. Meta-analysis was performed to evaluate the pooled effect estimate of intervention of SHED by Review Manager 5.4.1. To investigate the therapeutic efficacy of SHED intervention, we also analyzed the test of heterogeneity (I2), overall effect (Z), sensitivity, and publication bias. Among the 2156 scrutinized studies, 40 were included and evaluated as per inclusion and exclusion criteria. The intervention of SHED and its derivatives in several diseases depicted statistically significant therapeutic effects in periodontitis, pulpitis, spinal cord injury, parkinson's disease, alzheimer's disease, focal cerebral ischemia, peripheral nerve injury, and retinal pigmentosa. SHED also improved levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin in liver fibrosis . In autoimmune diseases also, values were significant. SHED also showed a statistically significant reduction of wound healing area and new bone formation in bone defects. The pooled effect estimates of included preclinical studies demonstrated a statistically significant therapeutic effect of SHED in numerous diseases. Based on our data, it is suggested that the potential of SHED may be implemented in clinical trials after conducting a few more preclinical studies.

1. Introduction

Over the decade, the impending benefits of the stem-cell-based approach as a regenerative medicine have been extensively examined and well-established. Based on the origin of isolation, stem cells can be classified into embryonic, induced pluripotent, and adult stem cells, including hematopoietic and mesenchymal stem cells [1], which can be easily identified and characterized by their unique surface marker protein from a cell repertoire. The ethical issues related to embryonic stem cells and the tedious technique involved in generating induced pluripotent stem cells have raised concerns regarding using these stem cells; thus, researchers have focused on adult stem cells, implicating them in various stem cell-based therapies.

Mesenchymal stem cells (MSCs) unveil enormous potentials such as self-renewal, multi-lineage differentiation, anti-inflammatory, and immunomodulation and, thus, applied in combating numerous life-threatening diseases. MSCs are fibroblast-shaped and characterized by the presence of CD105, CD73, and CD90, the absence of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR cell surface markers [2]. The numerous repertoire of MSCs in adults is bone marrow, umbilical cord, amniotic fluid, wharton's jelly, adipose tissue, menstrual blood, and teeth. We can categorize dental stem cells into various types based on their location, including periodontal ligament stem cells (PDLSCs), dental follicle progenitor cells (DFPCs), stem cells from apical papilla (SCAPs), dental pulp stem cells (DPSCs), and stem cells from human exfoliated deciduous teeth (SHED) [3].

Stem cells from human exfoliated deciduous teeth (SHED) are the adult stem cell population from exfoliated teeth' remnant, as

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Abbreviations

AD	‘ 'Alzheimer's disease
ABC	Alveolar bone crest
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
AST	Aspartate aminotransferase
BBB	Basso, Beattie, and Bresnahan
BMSCs	Bone marrow stem cells
CM	Conditioned medium
CEJ	Cementoenamel junction
MDT	Motor disability test
MSCs	Mesenchymal stem cells
ORT	Object recognition test
PD	Parkinson's disease
PBS	Phosphate buffer saline
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RA	Rheumatoid arthritis
RP	Retinal pigmentosa
RCTs	Randomized controlled trials
SCI	Spinal cord injury
SFI	Sciatic functional index
SLE	Systemic Lupus Erythematosus
SHED	Stem cells from human exfoliated deciduous teeth
SHED-CM	Stem cells from human exfoliated deciduous teeth-Conditioned medium

Miura et al. first reported in 2003. They harbored the stem cells from the pulp of exfoliated teeth and coined the term- SHED [4]. SHED unveil similar morphological and biological features to DPSCs and bone marrow stem cells (BMSCs) as they are fibroblast-shaped and express MSCs and neuroectodermal cell surface markers. However, *in vivo* research demonstrated that SHED entails higher proliferative potential and cell-population doublings than DPSCs [5]. SHED obtained from exfoliated teeth are otherwise a waste product and are a better alternative source of adult stem cells in regenerative medicine owing to less ethical concerns, non-invasive nature of harvesting, easily accessible, cost-effective, high no. of progenitor population, higher clonogenicity, higher proliferative potential [6], and differentiation potential into numerous cell types: hepatocytes, osteoblasts, odontoblast, chondrocytes, skin, neural, and myocytes cells [7] makes SHED an excellent source of adult stem cells.

The ameliorative potential of human adult mesenchymal stem cells in preclinical and clinical trials is well-acquainted in several fields such as liver fibrosis, periodontitis, spinal cord injury (SCI), pulpitis, parkinson's disease (PD), alzheimer's disease (AD) and retinal pigmentosa (RP) [8]. As asserted above, SHED embraces MSCs potential and offers pre-eminence over other types of MSCs therefore, to ascertain the ability of SHED in numerous diseases, we performed a systematic review and meta-analysis of SHED, SHED-conditioned medium (CM), and SHED-derived exosomes transplantation in disease-specific mouse models. The present exploration of SHED in concerned diseases would stipulate its beneficial upshots and give better insight into initiating and exploiting SHED as regenerative medicine.

2. Materials and methods

The study was designed and performed according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [9] and Cochrane Handbook guidelines.

2.1. Literature search and search strategies

Two independent investigators completed the comprehensive data extraction and analysis of the therapeutic potential of SHED in regenerative medicine. Following the inclusion and exclusion criteria, they searched different online databases including PubMed, Cochrane Library, Scopus, Google Scholar, Embase Medline, Web of Science and National Library of Medicine. The researchers carefully searched the research studies using various combinations of several keywords such as “mesenchymal stem cell transplantation” or “SHED”, “Stem cells from Human Exfoliated Deciduous teeth,” or “Mesenchymal Stem Cells”, “Deciduous teeth”, “Dental Stem Cells”, or “Hepatic fibrosis”, or “Liver fibrosis”, or “Liver diseases” or “regenerative dentistry”, or “pulpitis”, or “whole tooth regeneration”, or “bio-root regeneration”, or “periodontitis”, “pulp regeneration”, or “neurodegenerative diseases”, or “spinal cord injury”, or “spinal cord contusion”, or “myelopathy”, or “parkinson disease”, or “alzheimer”, or “focal cerebral ischemia”, or “nerve injury”, or “retinal pigmentosa's", or “rheumatoid arthritis”, or “multiple sclerosis”, or “stroke”, “rats","animal model"", or “wister, rats,”, or “mice”. We imported the included studies into Review Manager software 5.4.1 of Cochrane and conducted the analysis. We managed the included studies using Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia.

2.2. Inclusion and exclusion criteria

We prepared and analyzed the present meta-analysis according to the Population (P), Intervention (I), Comparator (C), Outcomes (O), and Study Design criteria for inclusion and exclusion. The population (P) included mice and rats.

Type of intervention (I): Human SHED only, SHED + collagen, induced or progenitors of SHED, SHED- CM, and SHED-exosomes. We compared the interventional groups with the sham groups, saline intervention, or only scaffolds.

Type of Outcome Measures (O): Regenerative ability of SHED analyzed via various outcomes measures such as microcomputed tomography (μ-CT) analysis [distance between the cementoenamel junction (CEJ) and alveolar bone crest (ABC)], bone volume/total volume percentage (BV/TV) %, microvessels formation, wound healing area, Basso, Beattie, and Bresnahan (BBB score), behavioural test, object recognition test (ORT), motor disability test (MDT), sciatic functional index (SFI), recognition index, Ca + imaging assay, and biochemical assays. Common outcome assessors were chosen for the same disease group to reduce the uncertainty and risk of bias.

Study design (S): Animals (mice and rats) model.

Language restrictions: We did not consider language restrictions.

Publication date restrictions: May 2003 (discovery of SHED) to January 2023.

Publication type: Full-text research, open access, and subscription type.

Exclusion criteria: Posters, pre-prints, review studies, studies illustrating the clinical significance of other dental stem cells in regenerative medicine, studies that have a single study on the desired disease, editorial or opinionated studies, studies that do not

have an appropriate control group or depicted wrong study design or animal with co-morbidities, usage of treatments were not documented correctly, or any risk of bias of included criteria, and duplicated studies.

2.3. Dealing with incomplete data

The curated results of meta-analyzed studies depend on the available data in the public domain. Thus, we have emailed the respective first author or corresponding authors to deal with incomplete or missing data from a study needed for meta-analysis. To reduce reporting bias from our end, we excluded studies if appropriate data were not collected or if the authors did not respond.

3. Data extraction and quality assessment

3.1. Data extraction

Two independent investigators searched and assembled the statistical data in Microsoft Excel, including mean, standard deviation (SD), standard error (SE), and the number of animals in the included studies. The investigators extracted the data by reviewing texts, images, and graphs. Additionally, the investigators collected study characteristics and information, including authors' details, title, year of study, journal/book/source, date of publication, volume, identifiers (PubMed and DOI ID), methods, population, intervention, comparisons, and outcome measures (included as per the disease).

4. Quality assessment

The quality assessment of the study reflects the methodological risk of bias in its methods and results. The risk of bias was assessed according to SYRICLE's standard risk of bias tool for animal studies [10]. Further, the “Gold Standard Publication Checklist to Improve the Quality of Animal Studies” was also considered for the quality assessment. Two independent investigators separately evaluated the internal quality process of included studies. If necessary, the investigators resolved discrepancies through discussion or sought assessment from a third independent investigator.

We included eight domains of the risk of bias scale for validating the quality of publication: (1) Sequence generation to evaluate the random allocation of animals, (2) Baseline Characteristics for selection bias assessment, (3) Animal Random housing to evaluate performance bias, (4) Random outcome assessment of the desired outcome for performance bias, (5) Blinding of assessor for an outcome to reduce the performance risk of bias, (6) Incomplete Outcome data for attrition bias (7) Selective outcome reporting to appraise reporting bias and (8) Other risks of bias of the included studies. The risk of bias was judged and answered as “high,” “low,” and “Unclear” if the study had clearly stated any risk of bias in the process, no risk of bias, and not stated or uncertain risk, respectively.

4.1. Data analysis

As animal studies depict primary concern of heterogenicity in study designing, thus, heterogenicity or I^2 was computed and illustrated as not significant (low), moderate, substantial, and considerably high if I^2 statistics are 0–40%, 30–60%, 50–90%, and 75%–100%, respectively, as per Cochrane guidelines. The random and fixed effect model concluded the overall effect estimate of studies. A fixed-effect model was used to analyze the effect size of an individual study on the overall effect. We excluded studies that contributed significant heterogeneity to the results. We performed the overall effect test calculation to analyze the intervention's effect compared to the vehicle group. We calculated the mean difference if the included studies used similar outcome measures. If the included studies had different follow-up or outcome measures, we calculated and compared their standardized mean difference. The fixed-effect model analyzed the heterogeneity and estimated the weighted effect of an individual study on the overall pooled effect estimates.

5. Results

5.1. Search results

We imported 2156 references to Covidence using different electronic databases, search engines and search criteria. Among the imported studies, 1068 were duplicates; hence, 1088 were reviewed and screened by their title and abstract. Out of the 1088 studies, we excluded 978 as they were unrelated to the designed meta-analysis and did not meet the exclusion criteria. After conducting a full-text assessment of the remaining 110 studies, we included 40 as they met the inclusion criteria [11–50]. Among the 70 excluded studies, 32 studies have different study designs; two studies were case reports of human clinical trials with 2 participants, 17 studies used different outcome measures than the included one, 11 studies have a wide variation in measuring scales of the outcome, six studies used animal models other than included population such rabbits and dogs, one study had different intervention while one study was pre-print. Fig. 1 depicts the PRISMA workflow of the searched and assessed studies.

5.2. Description of included study

Out of the 40 included studies, we categorized 15 studies in the ND section, two studies in the retinal section, four studies in liver-related diseases, four studies in the AD section, three studies in wound healing sections, five studies related to bone regeneration, and the remaining six studies in tooth-related diseases. Table 1 summarizes the number of studies and animals in various conditions. Table 2 provides detailed characteristics of the 40 animal studies in our meta-analysis, including information on animal models, outcome measures, form of SHED treatment, and intervention follow-up. We utilized Covidence software for comprehensive data extraction, and documented the details such as the author's name, institution, setting, and funding source of the included studies, which are provided in Supplementary Table 1.

5.3. Assessment of risk of bias

Table 3 s the risk of bias per SYRICLE's Risk of Bias tool (RoB tool) for animal studies; however, while all studies stated their compliance with animal handling and ethical guidelines, the analyses did not specify the random housing and environmental conditions. Among the 40 included studies, only 17 provided statements regarding random housing. The significant risk of bias in 40 included studies was exhibited in performance bias, as 13 studies narrated blinding of outcome assessors, and only five studies unveiled random allocation for outcome assessments. In tooth-related anomalies, the included studies depicted blinding as unclear, and one study revealed a high risk in selective outcome reporting. We considered four studies from the ND section, two from the RP section, and two from the wound healing sections as high risk in another domain of bias. This determination was made based on the fact that these studies were authored by the same authors, as shown in Table 3. Among the 40 included studies, six

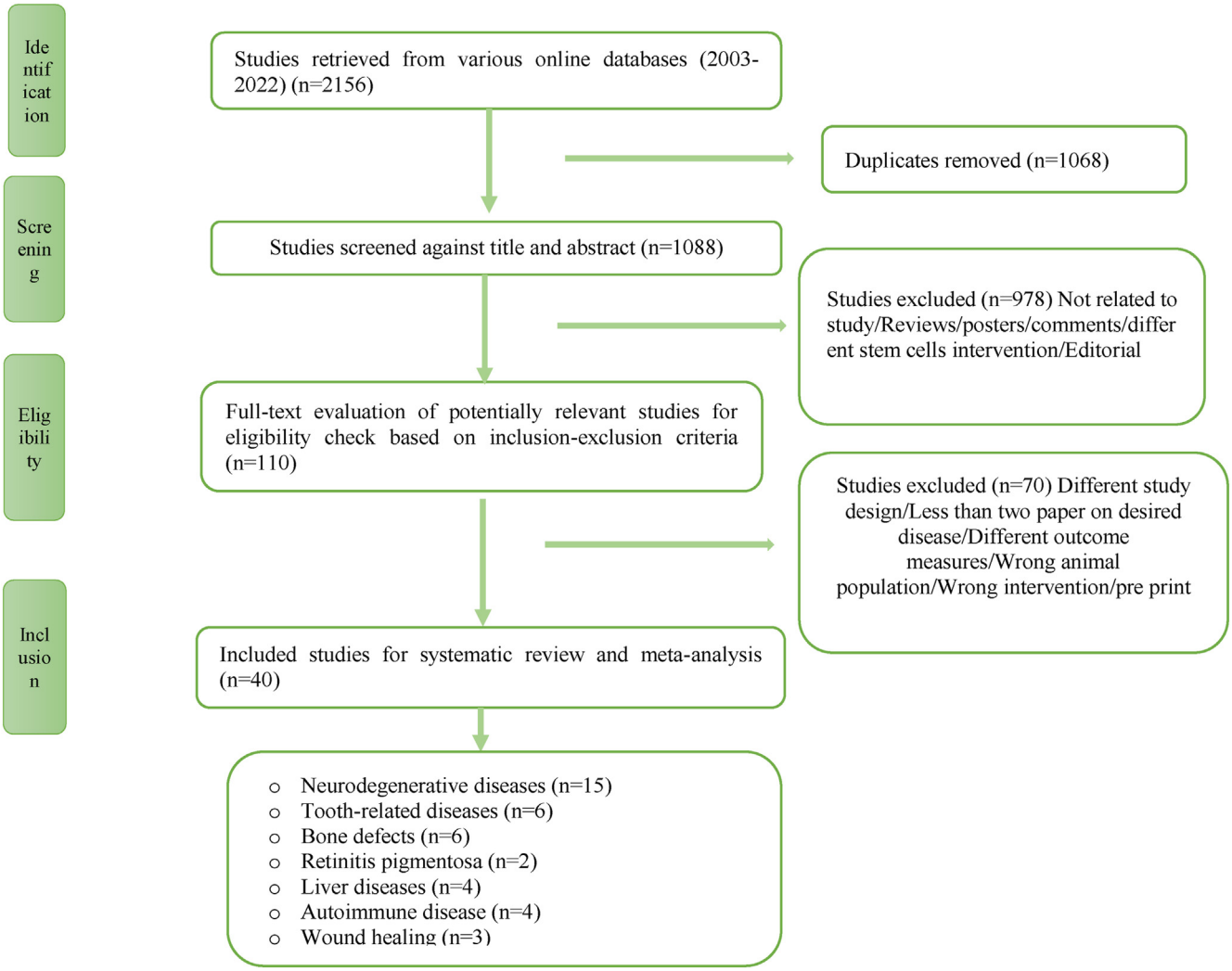


Fig. 1. PRISMA flow chart: the detailed flow diagram of study selection, screening, and inclusion process according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).

from Periodontitis, SCI, liver failure, and bone defect sub-sections depicted a high risk of bias in selective methods. The 40 studies exhibited 61.25% low risk, 34.4% unclear risk, and approximately 5% high risk in all domains. To reduce the risk of biasness among the studies, we tried to include the same outcome from all the studies instead of considering every outcome. Including every outcome from a single study would have made the analysis more cumbersome.

6. Meta-analysis

6.1. Neurodegenerative diseases and nerve injury

For neurodegenerative disorders, data were classified into five diseases viz. SCI, PD, AD, focal cerebral ischemia (FCI), and peripheral nerve injury (PNI). Five studies were included to evaluate SHED in SCI, consisting of one hundred eleven thoracic laminectomy animal models. In one [18] of the five included studies, SHED-CM was injected while in remaining SHED were injected at the injury site. The meta-analysis data demonstrated in Fig. 2a unveiled a significant improvement in BBB score at six weeks of follow-up in SHED compared to control Phosphate Buffer Saline (PBS). The BBB score outcome assessed, exhibited MD = 6.12 [95% CI = 5.21 to 7.03 test of heterogenicity I^2 = 59%, p = 0.05, Overall effect Z = 13.14, p-value 0.00001]. For meta-analysis of regenerative ability as shown in Fig. 2b of SHED in PD, three studies [23–25] comprising fifty-four 6-ODHA induced ' 'parkinson's models were analyzed for behavior after six weeks. The behavioral test data analysis depicted Mean Difference (MD) = −1.65 [95% CI = −2.33 to −0.97, test of heterogenicity I^2 = 10%, p = 0.33, Overall effect Z = 4.75, p-value 0.00001]. A study [26] (Fig. 2c) pertaining to twenty $A\beta_{1\text{-}40}$ induced ' 'alzheimer's animal models accounted for the statistically significant ameliorative effect of SHED in AD {MD = 20.40 [95% CI = 15.45 to 25.35, the test of heterogenicity: not applicable, Overall effect Z = 8.08, p-value 0.00001]}.

In FCI, motor disability score was assessed two weeks after the SHED [27] and SHED-CM treatment [50], the meta-analysis data (Fig. 2d) reveals the statistically significant regenerative ability of SHED intervention in FCI (MD = −2.95 [95% CI = −3.97 to −1.92, the test of heterogenicity I^2 = 0%, p = 0.57, Overall effect Z = 5.66, p-value 0.00001]). The treatment of SHED-CM exhibits greater regenerative potential that is MD = -3.25 [95% CI: 4.72 to −1.78] in comparison to SHED treatment MD = −2.66 [95% CI: 4.08 to −1.24]. For PNI, the SFI as an outcome was assessed for the meta-analysis. For the analysis of SHED treatment in PNI, eighteen sciatic excised animal models were used.

After six weeks of treatment, study analyzed the overall effect of SHED and found that meta-analyzed data indicated a statistically

Table 1
Studies and number of animals in intervention groups: Detailed information of the number of studies categorized into tooth -related diseases, neurodegenerative diseases, autoimmune diseases, wound healing, liver and retinal injury with respect to the number of animals in interventions measures.

Target field	No. of studies	Number of animals Control	Intervention	Total
1.Neurodegenerative diseases and Nerve injury	**15**	**108**	**110**	**218**
1.1Spinal Cord Injury	6	56	55	**111**
1.2Parkinson's Disease	1	26	28	**54**
1.3Alzheimer's disease	2	10	10	**20**
1.4Focal Cerebral Ischemia	3	7	8	**15**
1.5Peripheral Nerve injury	3	9	9	**18**
2.Retinitis pigmentosa	**2**	**18**	**18**	**36**
3.Acute Liver Failure & Liver Fibrosis	**4**	**23**	**25**	**48**
4.Autoimmune disease	**4**	**47**	**47**	**94**
4.1Rheumatoid arthritis	2	14	14	**28**
4.2Systemic Lupus Erythematosus	2	33	33	**66**
5.Wound healing	**3**	**16**	**16**	**32**
6.Bone defects	**6**	**34**	**34**	**68**
6.1Orofacial Congenital anomalies	3	16	16	32
6.2Calvaria defect	2	11	11	22
6.3Post-menopausal osteoporosis	1	7	7	14
7.Tooth related diseases	**6**	**34**	**35**	**69**
7.1periodontitis	3	23	23	46
7.2root loss	1	3	3	6
7.3pulpitis	2	8	9	17
Total	**40**	**280**	**285**	**565**

Bold characters in tables are the seven broad categories of diseases included in meta-analysis which were further sub-divided also it directly provide the information of no. of studies and total animals included in the broad categories of diseases.

significant impact of SHED in the sciatic excised model. The intervention's overall effect of the three studies is MD = 6.95 [95% CI = 3.61 to 9.58, test of heterogenicity I^2 = 0%, p = 0.87, Overall effect Z = 4.33, p-value 0.0001]. Data from two studies were analyzed in PNI as the study by Santos et al., 2019 assessed the outcome after three weeks and three days. Thus, contributing significant heterogenicity to the included studies and alteration in standard mean difference.

6.2. Retinitis pigmentosa

Thirty-six RPGR-knockout animal models, were analyzed for Ca + imaging assay and electroretinogram to evaluate the effect of SHED treatment on retinal degeneration [34,35]. The meta-analyzed data showed the significant potential of SHED treatment as depicted in Fig. 3 (SMD = 2.95 [95% CI = 1.94 to 3.96, test of heterogenicity I^2 = 0%, p = 0.83, Overall effect Z = 5.71, p-value 0.00001]. The included studies didn't show a statistically significant difference in heterogenicity; however, the contributing authors of both studies are common, thus, indicating a risk of potential publication bias.

6.3. Acute liver failure & liver fibrosis

SHED's role in liver treatment was analyzed using four studies [33–36], accompanying forty-eight CCl4-induced chronic liver fibrosis. The models were infused with SHED-hepatocytes,SHED-CM and Control (PBS). The meta-analysis data were extracted and evaluated for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels with a follow-up period of 24hrs. to 8 weeks. The magnitude of ALT level showed a significant decrease (Fig. 4a) in the SHED group in comparison to vehicle Standard Mean Difference (SMD) = −4.14 [95% CI = −7.36 to −0.92, test of heterogenicity I^2 = 82%, p = 0.004, Overall effect Z = 2.52, p-value 0.001]). Matsushita *et al.* 2017 study contributed significant heterogenicity to the pooled-effect estimates.

The magnitude of AST decreases significantly and favors the treatment of SHED-hepatocytes and SHED-CM compared to control (PBS) when infused in liver fibrosis-induced mice. Hirata et al., 2016 had shown significant changes in results and, thus, were not involved in generating forest plots. Fig. 4b represents the investigated result of the data. (SMD = −1.21 [95% CI = −2.08 to −0.34, test of heterogenicity I^2 = 0%, p = 0.58, Overall effect Z = 2.72, p-value 0.007]). As shown in Fig. 4c, the treatment of SHED also ameliorates the bilirubin level. (SMD = −5.09 [95% CI = −7.02 to −3.15, test of heterogenicity I^2 = 0%, p = 0.63, Overall effect Z = 5.15, p-value 0.00001]). Overall, in the mouse model, the administration of SHED-hepatocytes and SHED-conditioned media (SHED-CM) resulted in the amelioration of liver fibrosis, as evidenced by improvements in AST, ALT, and bilirubin outcomes.

6.4. Autoimmune disease

The AD section is categorized into two subgroups as per the available studies: Rheumatoid arthritis (RA) and Systemic Lupus Erythematosus (SLE). To comprehend the therapeutic role of SHED in RA, we performed a pooled analysis of data extracted from twenty-eight Collagen-induced Arthritis (CIA) animal models generated from two studies. The score outcome data of disease severity was determined after two weeks of SHED injection into fourteen animal models compared to the control (PBS treated). Meta-analyzed data (Fig. 5a) examined through a fixed-effect model indicated that the treatment of SHED significantly improved disease severity score (MD = −5.99 [95% CI = −6.67 to −5.31, test of heterogenicity I^2 = 99%, p < 0.00001, Overall effect Z = 17.37, p-value 0.00001]). Although SHED treatment showed a statistically significant effect, the included studies detected a high level of heterogenicity.

Similar to RA, the overall beneficial effect of SHED in SLE was analyzed [43,44] and evaluated in studies that entailed sixty-six animal models [thirty-three SHED treatment and thirty-three Control (PBS) animal models]. After injecting 0.1 x 106 cells/10g of body weight SHED into the tail vein, study analyzed the biochemical assays after 20 weeks. The data analyzed using random

Table 2
Characteristics of included studies: Summary of included studies and their categorization into tooth -related diseases, neurodegenerative diseases, autoimmune diseases, wound healing, liver and retinal injury.

Characteristics of Included studies								
Author	Model of animal/Age/Sex/Weight	Intervention type		Dose of SHED or Shed-derived interventions	Route of delivery	Measurement time for outcome assessment (weeks)	Outcome measures	References
A. Tooth-related Diseases								
1. Periodontal regeneration								
Gao et al., 2018	Silk-ligature induced periodontal defect model of Sprague Dawley rats/ND[a]/M[b]/220–250 g	SHED[c]	Phosphate Buffer Saline	1 X 10^6 cells	injected once a week into mesial and distal regions of the palatal side of the second molar	Four week	μ-CT[d] analysis (distance between CEJ[e] and ABC[f])	[13]
Wei et al., 2020	CD[g]-1 mice with Silk ligature induced periodontal defect model/9–10 months old/M[b]/ND[a]	SHED[c]	Phosphate Buffer Saline	1 X 10^6 cells	Once a week buccal and lingual side of the first molar was injected	Two week	μ-CT[d] analysis (distance between CEJ[e] and ABC[f])	[14]
Wu et al., 2019	periodontal defect model 4 × two × 1.5 mm^3 at the buccal alveolar bone of Sprague Dawley rats/8 week/M[b]/	β-TCP[g] scaffolds + SHED[c]-exosomes	Phosphate Buffer Saline	100 μg exosomes with 1 mg β-TCP[g] scaffolds	Implanted at defect sites	Four weeks	μ-CT[d] analysis (BV[h]/TV[h])	[15]
2. Root regeneration								
Yang et al., 2019	Orthotopic model/12-weeks-old/M[b]/ND[a]/ND[a]	Treated Dentin Matrix + SHED[c]	Treated Dentin Matrix	Cell sheet	Implanted into jawbones	Eight weeks	Measurement of thickness of fibers	[16]
3. Pulp regeneration								
Cordeiro et al., 2008	B.17 SCID[i] immunodeficient mice/5-7 weeks-old/M[b]/ND[a]	Tooth scaffold + SHED[c]	Tooth scaffold + Alpha MEM[j]	8 X 10^5 cells	implanted bilaterally into dorsum subcutaneous tissue	Four weeks	Micro vessels/HP field	[17]
de Cara et al., 2019	Rodent orthotopic model/10 weeks old/ND[a]/ND[a]	SHED[c]-CM[k]	Untreated	Not defined	Applied on blot clot on root canal opening site	Four weeks two days	Matrigel angiogenesis assay	[18]
B. Neurodegenerative disease or Nerve Injury								
1. Spinal Cord Injury								
Nicola et al., 2016	Sprague-Dawley rats with Spinal Cord Injury (SCI) at T9 thoracic vertebral level/Two months/M[b]/250–280 g	SHED[c]	Untreated	3 × 10^5 cells	Injected to the injury site	Six weeks	BBB[l] Score	[19]
Golshan et al., 2018	Sprague-Dawley rats with Spinal Cord Injury (SCI) at T7 thoracic vertebral level/Two months/M[b]/250–280 g	SHED[c]-CM[k]	Collagen hydrogel	3 μl	Injected to the injury site	Six weeks	BBB[l] Score	[20]
Nicola et al., 2017	Sprague-Dawley rats with Spinal Cord Injury (SCI) at T9 thoracic vertebral level/Two months/M[b]/250–280 g	SHED[c]	Untreated	3 × 10^5 cells	Injected to the injury site	Six weeks	BBB[l] Score	[21]
Nicola et al., 2019	Sprague-Dawley rats with Spinal Cord Injury (SCI) at T9 thoracic vertebral level/Two months/M[b]/250–280 g	SHED[c]	Untreated	3 × 10^5 cells	Injected to the injury site	Six weeks	BBB[l] Score	[22]
Sakai et al., 2012	Sprague-Dawley rats with Spinal Cord Injury (SCI) at 9th–11th thoracic vertebral level/Adult/Female/ND[a]	SHED[c]	Phosphate Buffer Saline	2 x 10^5/μl and 2.5 μl at each site	Injected to the injury site	Eight weeks	BBB[l] Score	[23]

Table 2 (*continued*)

Characteristics of Included studies								
Taghipour et al., 2012	Sprague-Dawley rats with Spinal Cord Injury (SCI) at 8th-11th thoracic vertebral level/ Adult/Female/250-300g	SHED[c]	Phosphate Buffer Saline	0.5 × 10^6 cells	Injected to the injury site	Seven weeks	BBB[l] Score	[24]
2. Parkinson's disease								
Fuji et al., 2015	Sprague-Dawley rats with 6 -OHDA induced Parkinson's/6-7-weeks-old/M[b]/250–350 g	SHED[c]	Phosphate Buffer Saline	2 x 10^5/μl and 2 μl at each site	Injected into striatum	Six weeks	Behavioral test	[25]
Wang et al., 2010	Sprague-Dawley rats with 6 -OHDA induced Parkinson's/8-weeks-old/Female/250–350 g	SHED[c]	Neurobasal Medium	2 x 10^5/μl and 2.5 μl at each site	Injected into striatum	Eight weeks	Behavioral test	[26]
Zhang et al., 2018	Sprague-Dawley rats with 6 -OHDA induced Parkinson's/6-7-weeks-old/M[b]/180–200 g	SHED[c]	Phosphate Buffer Saline	1 x 10^5/μl and 2.5 μl at each site	Injected into striatum	Eight weeks	Behavioral test	[27]
3. Alzheimer's Disease								
Mita et al., 2015	$A\beta_{1-40}$ induced Alzheimer's model/9-weeks-old/M[b]/35-37g	SHED[c]-CM[k]	DMEM	50 μl	Administered intranasally	Five weeks	Recognition Index	[28]
4. Focal Cerebral Ischemia								
Inoue et al., 2013	Sprague-Dawley rats with Cerebral ischemia Model/Adult/M/350-400g	SHED[c]-CM[k]	DMEM	100 μl	Administered intranasally	Two weeks	MDI[m]	[29]
Sugiyama et al., 2014	Sprague-Dawley rats with Cerebral ischemia Model/Adult/M[b]/350-400g	SHED[c]	Phosphate Buffer Saline	1 x 10^6 cells	Injected into striatum	Two weeks	MDI[m]	[30]
5. Peripheral Nerve Injury								
Beigi et al., 2014	Excision and removal of 13 mm segment of Sciatic nerve removed /ND[a]/Wistar Male rats/ 250-300g	PCL/gel nanofibrous + SHED[c]	PCL/gel nanofibrous	1 x 10^5 cells	Implantation of nerve guide	Twelve weeks	SFI[n]	[31]
Santos et al., 2019	Excision and removal of 7 mm segment of Sciatic nerve/ND[a]/ Wistar M[b] rats/250g	Poly (lactide-co-glycolide)(PLGA) + SHED[c]	Poly (lactide-co-glycolide)(PLGA)	1.2 X 10^5 cells	Implantation of nerve guide	Three weeks three days	SFI[n]	[32]
Wakayama et al., 2015	Excision and removal of 10 mm segment of Sciatic nerve/7-8-weeks-old/Wistar M[b] rats/250-300g	SHED[c]-CM[k]	DMEM	Not defined	Implantation of nerve guide	Twelve weeks	SFI[n]	[33]
C. Retinitis pigmentosa								
Li et al., 2019	RPGR-knockout C57/ BL6J mice/3–4 months/ ND[a]/ND[a]	SHED[c]	Balanced medium	Two × 10^4 cells	Injection into the sub-retinal space region	Three weeks four days	Ca + imaging assay	[34]
Li et al., 2019	RPGR-knockout C57/ BL6J mice/4 months/	SHED[c]	Balanced medium	Two × 10^4 cells	Injection into the sub-retinal space region	Two month	Electroretinogram	[35]
D. Acute Liver Failure & Liver Fibrosis								
Yuniartha et al., 2021	C57BL/6, CCl4-treated chronic liver fibrosis model mice/6-weeks-old/Female/ND[a]	SHED[c] derived Hepatocytes	Phosphate Buffer saline	1 x 10^6/10 g m of body weight	Intra-splenically infused	Eight weeks	ALT[o], AST[p] and Bilirubin levels	[36]
Takahashi et al., 2019	C57BL/6, CCl4-treated chronic liver fibrosis model mice/6 –8 weeks/M[b]/ND[a]	SHED[c]-converted hepatocyte-like cells	Not received any intervention	1 x 10^6 cells/ spheroids	Implantation into the linear fissure on the lateral lobe of the left liver	Four weeks	ALT[o], AST[p] and Bilirubin levels	[37]
Hirata et al., 2016	C57BL/6J mice CCl4-treated chronic liver fibrosis/6 weeks/ female/ND[a]	SHED[c]-CM[k]	DMEM[q]	500ul	Injected into a Jugular vein	One day	ALT[o], AST[p] and Bilirubin levels	[38]
Matsushita et al., 2017	D-galactosamine treated Acute liver failure Sprague-Dawleyrats model/ female/200–250g	SHED[c]-CM[k]	DMEM[q]	1 ml	Injected into a Jugular vein	Seven days	ALT[o], AST[p] and Bilirubin levels	[39]

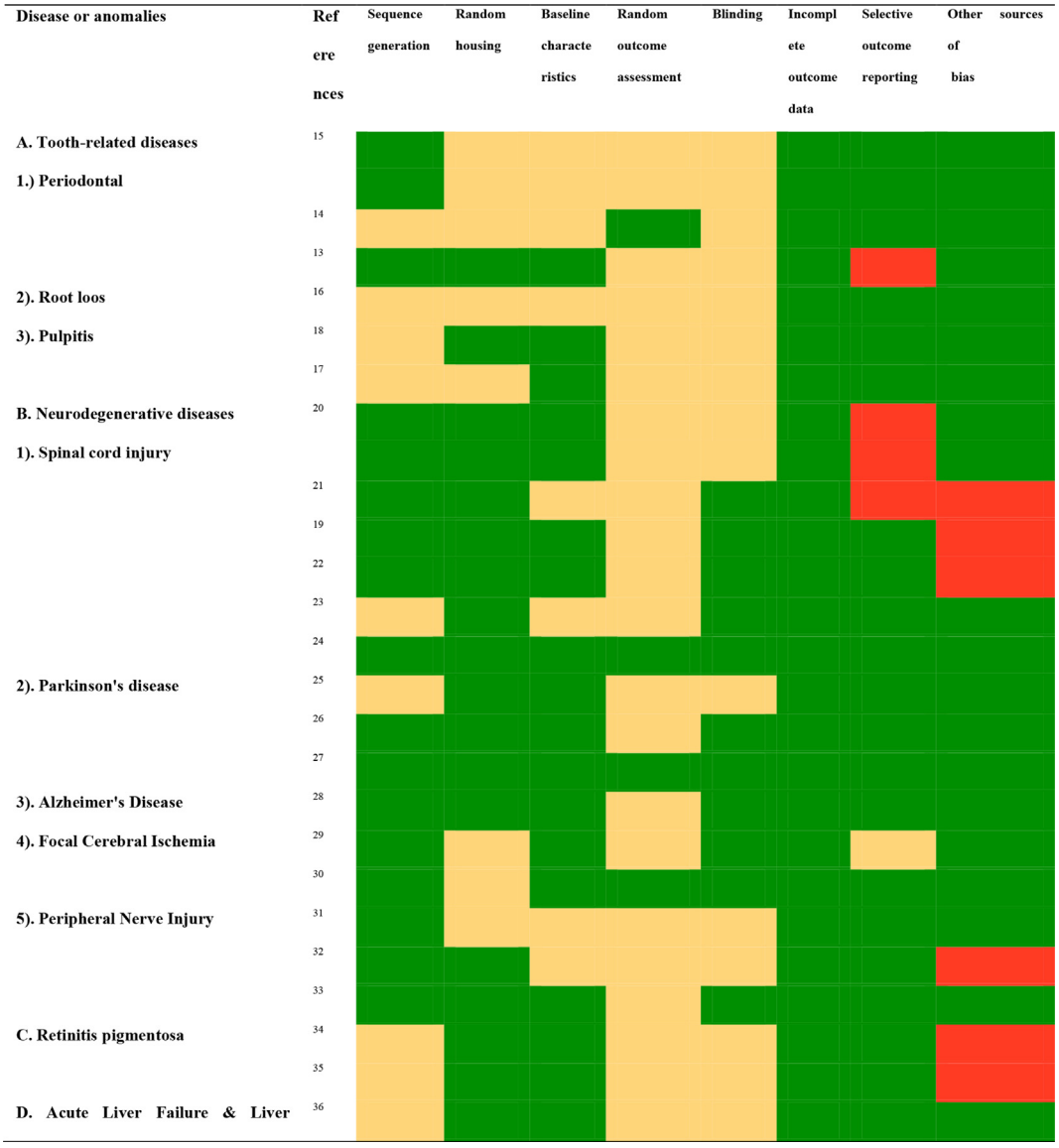
(*continued on next page*)

Table 2 (*continued*)

Characteristics of Included studies								
E. Bone Defect								
1. Orofacial Congenital anomalies								
Nakajima et al., 2018	BLAB/c-n mice with Calvaria defect (4 mm)/ ND[a]/ND[a]/ND[a]	PLGA + SHED[c]	Phosphate Buffer Saline	Not defined	implanted at the defect site	Twelve weeks	μ-CT[d] analysis (BV/TV[h])	[40]
Hiraki et al., 2020	BLAB/c-n mice with Calvaria defect (4 mm)/ ND[a]/ND[a]/ND[a]	SHED[c] + Atelocollagen sponge	Atelocollagen sponge	1 X 10^5 cells	Implanted at the defect site	Eight weeks	μ-CT[d] analysis (BV/TV[h])	[41]
Ogasawara et al., 2020	Temporomandibular Joint Osteoarthritis/11-week-old/M[b]/ND[a]	SHED[c]-CM[k]	DMEM[q]	0.5 ml	Injected into the tail vein	Ten days	μ-CT[d] analysis (BV/TV[h])	[42]
2. Calvarial Defect								
Rikitake et al., 2021	BLAB/c-n mice with skull defect (5 mm)/ ND[a]/ND[a]/ND[a]	SHED[c] + Atelocollagen sponge	Alpha-MEM + Atelocollagen sponge	1 X 10^5 cells	Implanted at the defect site	Eight weeks	μ-CT[d] analysis (BV/TV[h])	[43]
Sattary et al., 2020	Skull defect (3 mm) Wistar rats/8week-old/ Female/160-180g	SHED[c] + Polycaprolactone/ gelatin/ nanohydroxyapatite	Untreated	5 × 10^3 cells/ cm^2	Implanted at the defect site	Twenty four weeks	μ-CT[d] analysis (BV/TV[h])	[44]
3. Post-menopausal osteoporosis								
Sonoda et al., 2020	Ovariectomized C57BL/ 6J mice/10-weeks old/ Female/ND[a]	SHED[c]	Phosphate Buffer Saline	0.1 x 10^6 cells/ 10g of body weight	Injected intravenously	Four weeks	μ-CT[d] analysis (BV/TV[h])	[45]
F. Autoimmune disease								
1. Rheumatoid arthritis								
Ishikawa et al., 2016	DBA/1 J mice with Collagen-induced Arthritis/M[b]/8 weeks/ ND[a]	SHED[c]-CM[k]	DMEM[q]	500ul of SHED[c] -CM[k]	Injected into the tail vein	Two weeks	Disease Severity score	[46]
Zhang et al., 2019	DBA/1 J mice with Collagen-induced Arthritis/M[b]/8 weeks/ ND[a]	SHED[c]	Phosphate Buffer Saline	1 x 10^6 cells	Injected into the tail vein	Two weeks and four weeks	Disease severity score	[47]
2. Systemic Lupus Erythematosus								
Yamaza et al., 2010	C57BL/6J and C3MRL-Fas lpr/J (MRL/lpr) mice/6-7-weeks-old/ Female/ND[a]	SHED[c]	Phosphate Buffer Saline	1x10^5 cells/10g body weight	Injected into the tail vein	Twenty weeks	Biochemical assay	[48]
Ma et al., 2012	C57BL/6J and Balb/cA-nu/nu mice/6-weeks-old/Female/ND[a]	SHED[c]	Phosphate Buffer Saline	0.1 x 10^6 cells/ 10g of body weight	Injected into the tail vein	Twenty weeks	Biochemical assay	[49]
G. Wound Healing								
Lv et al., 2017	Sprague-Dawley rats Diabetic model with 4 mm skin excision of right hind feet/ND[a]/ ND[a]/180 to 200 g	SHED[c]	Phosphate Buffer saline	1.2 X 10^6 cells	Injection at the wound site	Two weeks	Wound healing area	[50]
Nishino et al., 2011	KSN/Slc nude mice with 8 mm skin excision on midline/7-weeks-old/ ND[a]/ND[a]	SHED[c]	Phosphate Buffer saline	1 X 10^6 on the wound site and 4 X 10^6 around the wound site	Applied at wound bed and injected intradermally around four sites of wound	Two weeks	Wound healing area	[51]
Nishino et al., 2011	KSN/Slc nude mice with 8 mm skin excision on midline/7-weeks- old/ ND[a]/ND[a]	SHED[c]	Phosphate Buffer saline	5 X 10^6 cells	Applied at the wound bed	Two weeks	Wound healing area	[52]

[a] Not-defined.
[b] Male.
[c] Stem cells from human exfoliated deciduous teeth.
[d] Micro microcomputed tomography.
[e] Cementoenamel junction.
[f] Alveolar bone crest.
[g] β-tricalcium phosphate.
[h] Bone volume/total volume percentage.
[i] Severe combined immunodeficiency.
[j] Minimum essential media.
[k] Conditioned Media.
[l] Basso, Beattie, and Bresnahan score.
[m] Motor disability index.
[n] Sciatic functional index.
[o] Alanine aminotransferase.
[p] Aspartate aminotransferase.
[q] Dulbecco's Modified Eagle Medium.

Table 3
Quality Assessments of included studies: Risk of bias assessment domains of forty included studies in various diseases (1) tooth-related diseases; (2) neurodegenerative diseases; (3) Retinitis Pigmentosa; (4) Liver failure and fibrosis; (5) Bone defect and (6) Wound healing.



effect model suggested that SHED intervention statistically decrease the Anti-Nuclear Antibodies (ANA) levels (SMD = −7.53 [95% CI = −12.50 to −2.57, test of heterogenicity I^2 = 62%, p = 0.10, Overall effect Z = 2.97, p-value 0.003]), creatinine levels (SMD = −7.77 [95% CI = −12.65 to −2.90, test of heterogenicity I^2 = 59%, p = 0.12, Overall effect Z = 3.12, p-value 0.002]) but does not improve anti ds-DNA levels (SMD = −18.04 [95% CI = −45.26 to 9.18, test of heterogenicity I^2 = 91%, p = 0.0010, Overall effect Z = 1.30, p-value 0.19]).

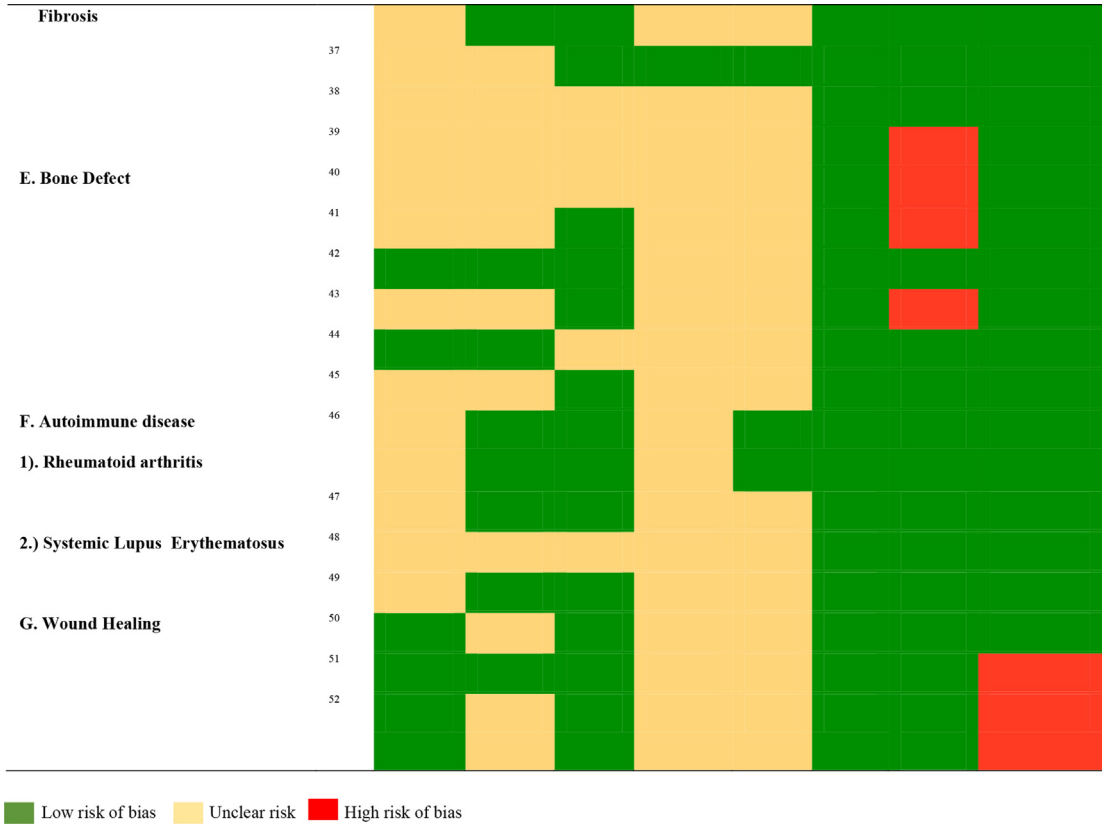
The overall effect, as depicted in Fig. 5b of SHED in SLE is SMD = −8.13 [95% CI = −11.47 to −4.79, test of heterogenicity I^2 = 69%, p = 0.007, Overall effect Z = 4.77, p-value 0.00001]) while, the test of subgroup showed less heterogenicity (I^2 = 0%, p = 0.76). The subgroup analysis showed a high level of heterogenicity in assessing the anti-ds-DNA level.

6.5. Wound healing

To illustrate the effectiveness of SHED in wound healing, we assessed studies including 16 groups treated with SHED and 16 groups treated with Control (PBS), all of which had excised skin [47–49]. The SHED-treated groups showed a statistically significant beneficial effect in decreasing wound healing, MD = −23.37 [95% CI = −34.48 to 12.27, test of heterogenicity I^2 = 94%, p = 0.0001, Overall effect Z = 4.13, p-value 0.00001]. The included studies also showed statistically significant heterogenicity p < 0.001, as depicted in Fig. 6.

6.6. Bone defect

We evaluated six studies to analyze the new bone formation capability of SHED. We assessed twenty-two calvaria defect animal



models to determine bone volume regeneration for orofacial bone anomalies such as cleft lip and palate [37,38]. Similarly, we evaluated ten calvaria defect animal models [39] to assess temporomandibular osteoporosis [39]. For the cleft and lip palate anomalies, SHED and scaffold were transplanted, while in temporomandibular joint osteoarthritis, SHED-CM was injected at the injury site. Fig. 7 represents the statistically significant effect of SHED in the formation of new bone volume in cleft and lip palate anomalies SMD = 1.76 [95% CI = 0.70 to 2.82, the test of heterogenicity I^2 = 0%, p = 0.89, Overall effect Z = 3.26, p-value 0.001]. Although temporomandibular joint osteoarthritis, the bone volume is not significantly elevated SMD = 1.26 [95% CI = −0.16 to 2.69, the test of heterogenicity I^2: not applicable, Overall effect Z = 1.73, p-value 0.08]. But, the overall impact of SHED in orofacial anomalies is statistically significant {SMD = 1.59 [95% CI = 0.74 to 2.44, test of heterogenicity I^2 = 0%, p = 0.85, Overall effect Z = 3.65, p-value 0.0003]} thus, suggesting the potential of SHED in bone repair. SHED treatment also depicted statistically significant bone formation in calvaria defect and post-menopausal osteoporosis MD = 16.71 [95% CI = 3.80 to 29.61, test of heterogenicity I^2:87% p-value 0.06, Overall effect Z = 2.54, p-value 0.01] and MD = 30.66 [95% CI = 21.22 to 40.10, test of heterogenicity I^2: not applicable, Overall effect Z = 6.36, p-value 0.00001] respectively.

6.7. Tooth-related diseases

We evaluated the pooled effect estimates of sixty-nine animal periodontal defect and orthotopic models. To analyze the efficacy of SHED or its derivatives, separate random effect analyses were conducted for periodontal regeneration, root loss, and pulp regeneration. The pooled-effect estimates of SHED compared to control (PBS) treatment in three studies of periodontal defects depicted significant improvement in ABC-CEJ distance and BV/TV percentage, as represented in Fig. 8a and b. Out of three studies, two studies [11,12] involved assessment of ABC-CEJ distance while one study [13] involved assessment of BV/TV percentage with SMD = −1.60 [95% CI = −2.53 to −067, test of heterogenicity I^2 = 0, p = 0.76, Overall effect Z = 3.36, p-value 0.00001] and SMD = 13.41 [95%CI = 8.69, 18.13, test of heterogenicity: not applicable, overall effect Z = 5.57, p-value 0.00001] respectively.

To analyze the regeneration potential of SHED in root loss, single study [14] was included, encompassing six orthotopic animal models. The models were transplanted with a SHED cell sheet combined with the treated dentin matrix and compared to the control (treated dentin matrix). The study concluded that the average expression of osteogenic-related marker OCN in the SHED intervention group was 141.46, while the expression was absent in the control. The intervention of SHED has shown significant odontogenic differentiation ability in root loss.

SHED also showed a statistically significant effect in treating pulpitis compared to control

We evaluated two studies, which consisted of seventeen animal models, for the aforementioned cases. In the study conducted by Cordeiro et al., 2008 [15], the models were treated with SHED and scaffold, and in another study experimentalized by de Cara et al., 2019 [16], the models were treated with SHED-CM. The outcome assessment underwent analysis in the fourth week after the treatment. The formation of micro-vessels was assessed, and found the MD = 4.27 [95% CI = 3.30 to 5.25 test of heterogenicity I^2 = 0, p = 0.90, Overall effect Z = 8.57, p-value 0.00001]. Fig. 8 demonstrates the funnel plots of the included studies.

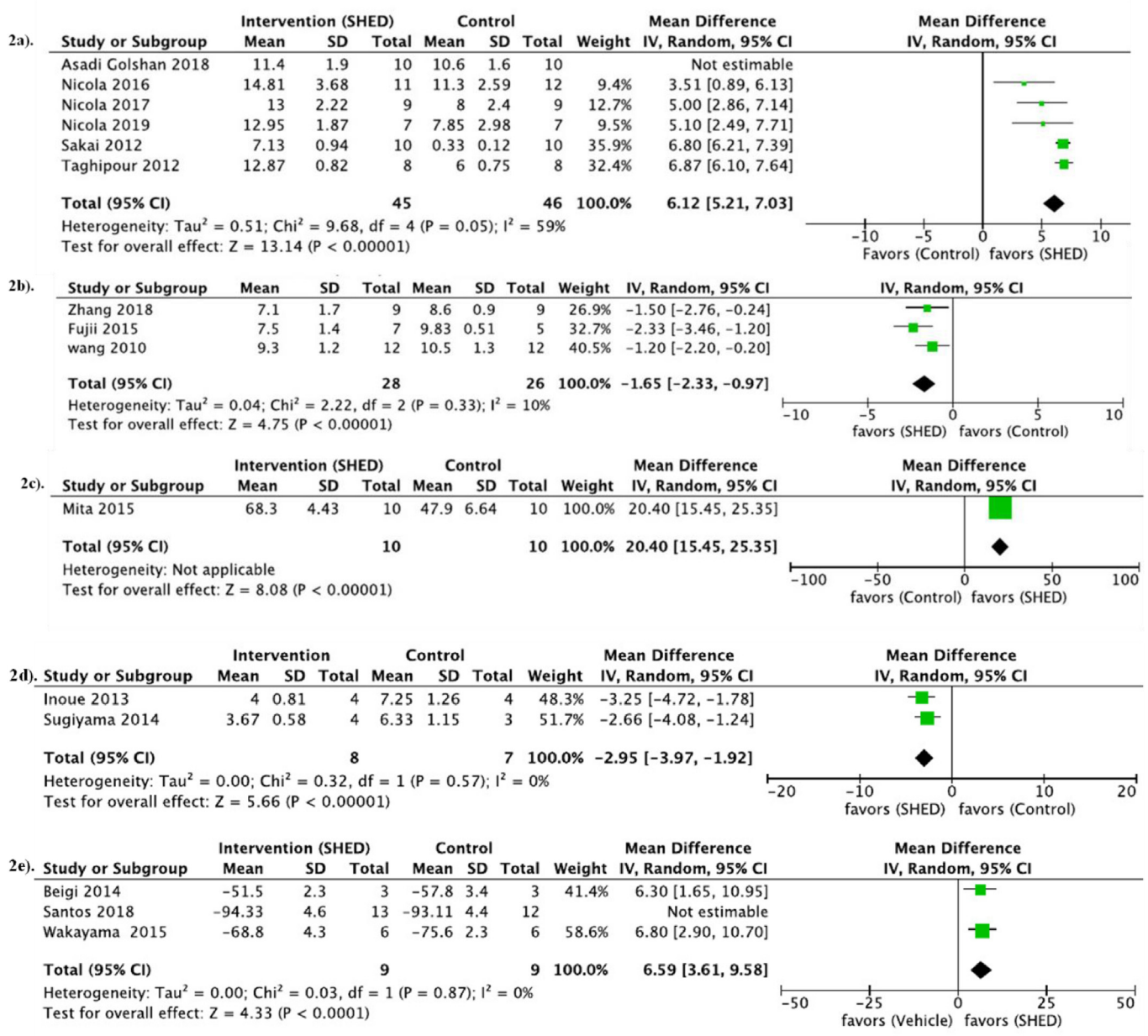


Fig. 2. Forest plot analysis in neurodegenerative disease: Depiction of SHED treatment effect in (a) Spinal cord injury, b) Periodontal defect, c) ' 'Alzheimer's disease, d) Focal cerebral ischemia and e) Peripheral nerve injury.

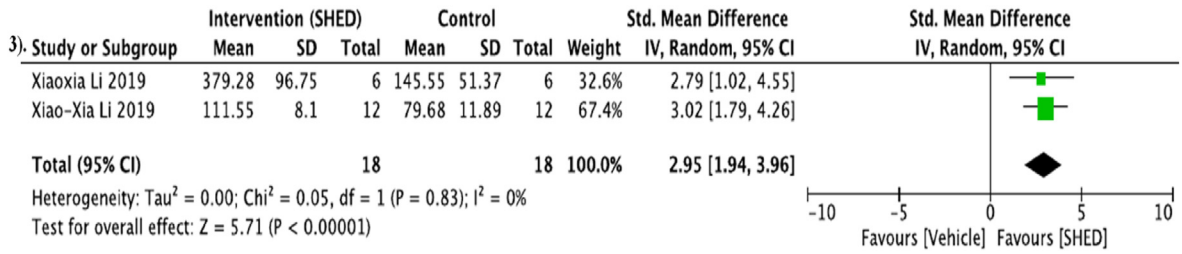


Fig. 3. Forest plot analysis in retinitis pigmentosa: The pooled-effect estimates of SHED treatment effect in Retinitis Pigmentosa showed a statistically significant effect in comparison to controls.

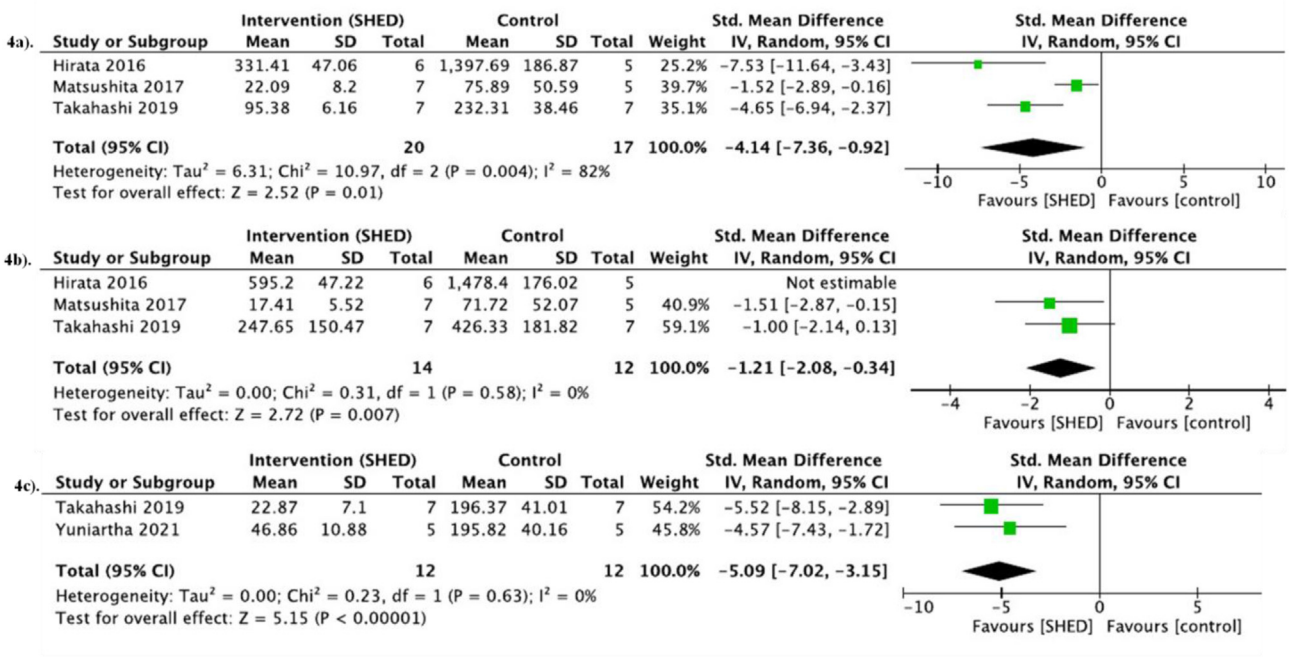


Fig. 4. Forest plot analysis in liver fibrosis and injury: SHED treatment depicted statistically significant effect in improvement of liver fibrosis and injury.

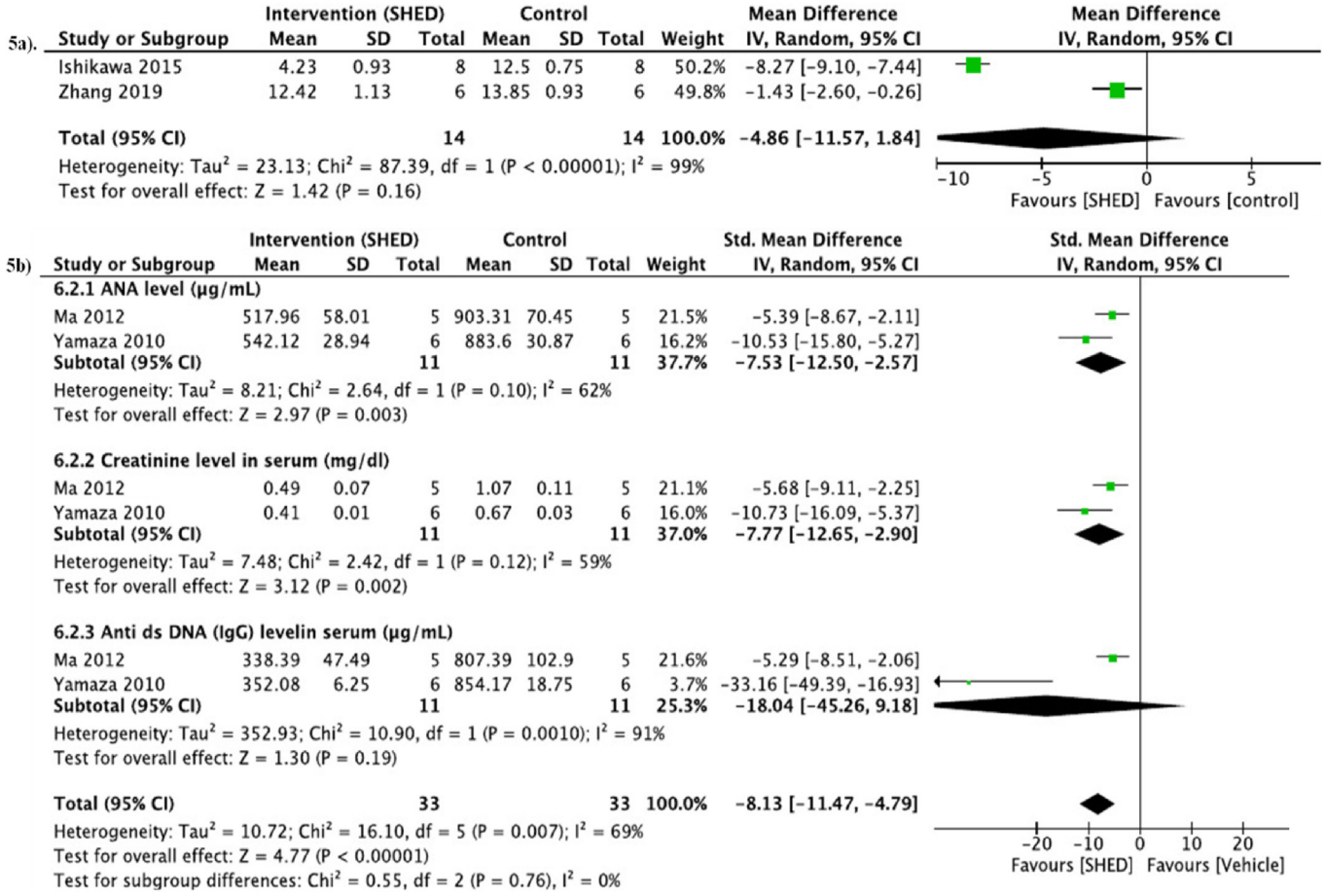


Fig. 5. Forest plot analysis in autoimmune diseases: The meta-analyzed funnel plot of SHED treatment depicted the significant pooled effect in (a) Rheumatoid Arthritis and (b) systemic lupus erythematous.

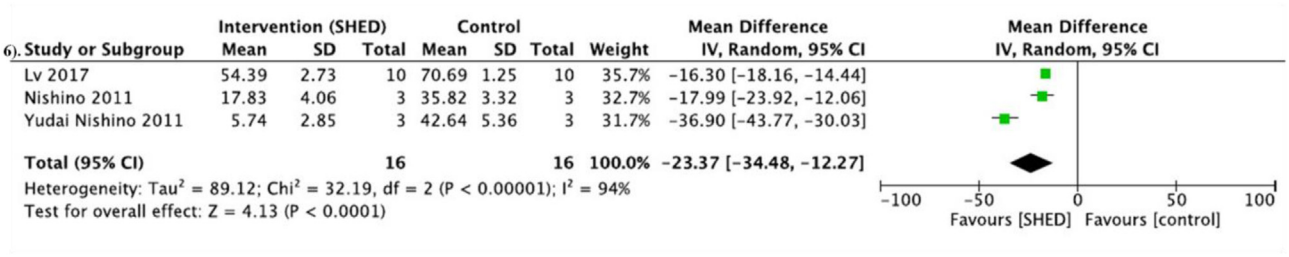


Fig. 6. Forest plot analysis in wound healing: SHED treatment showed statistically significant improvement in wound healing area.

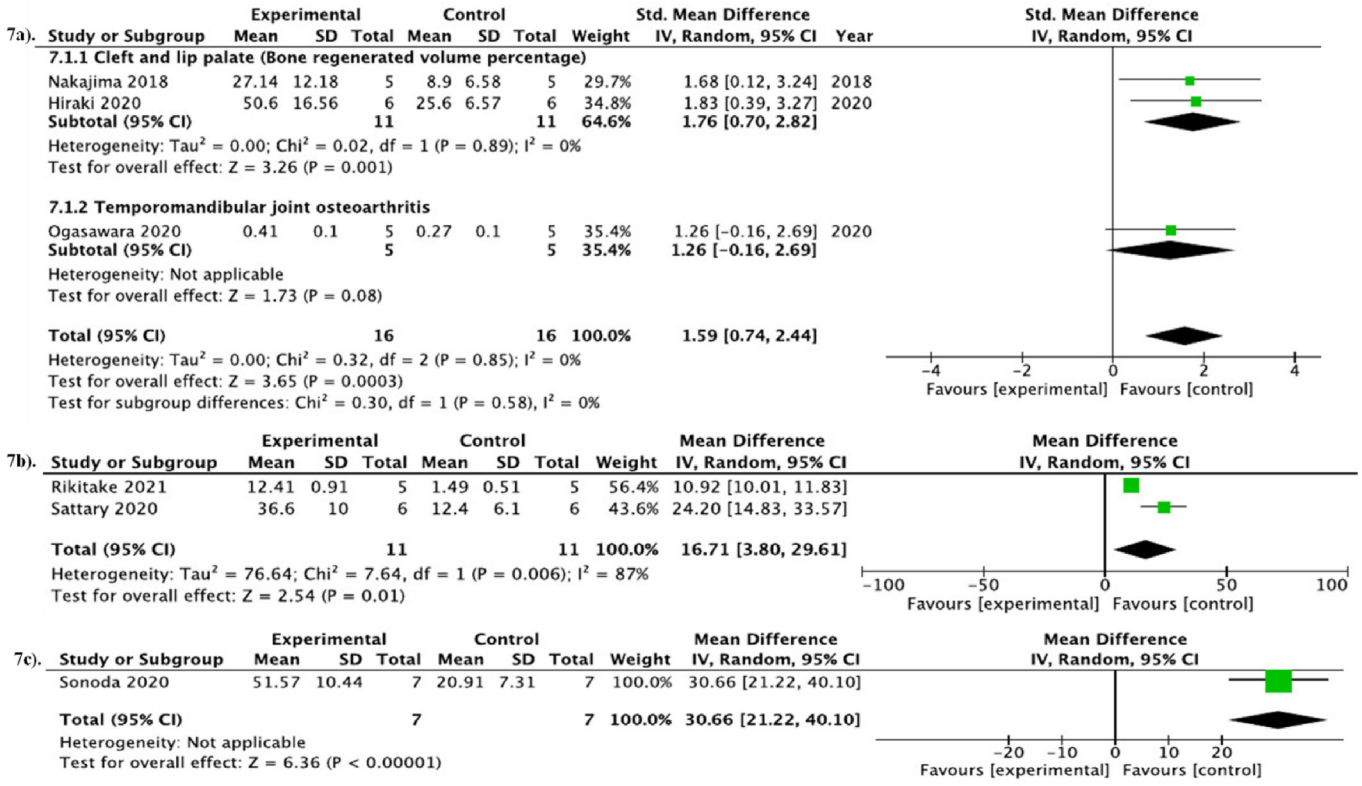


Fig. 7. Forest plot analysis in bone defect: Representation of SHED intervention effect a) Orofacial anomalies b) calvaria defect c) Temporomandibular joint osteoarthritis in bone defect section.

7. Publication bias and sensitivity analysis

Although the included studies assessing the potential of SHED as regenerative medicine in different diseases are less than 10, we still tried to evaluate robustness in pooled effect estimates. For the aforementioned, sensitivity analysis of included studies was computed with Review Manager 5.4.1. The included studies employed a fixed-effect model, and the formation of funnel plots involved SE (SMD) or SE (MD) on the y-axis and SMD or MD on the x-axis. To analyze the individual bias of each study on the overall effect estimate, we performed a leave-one-out sensitivity analysis method for the included studies. The included studies in tooth-related diseases, as demonstrated in Fig. 9,didn't show potential publication, with a p-value of 0.76 in the periodontitis subsection and a p-value of 0.90 for pulpitis disease. Studies evaluated in neurodegenerative sections such as PD, FCI, and PNI did not depict potential bias with a p-value of 0.33, 0.57, and 0.87. In contrast, the included studies in the SCI subsection showed statistically significant biases with a p-value of 0.05 as the three included studies [18,20,21] correspond to the same author in the SHED regenerative potential in SCI. Similarly, studies included for Retinal degeneration did not show publication bias (p-value 0.83).

The studies included for the assessment of ALT levels in liver injury exhibited high sensitivity (p value = 0.004) as the data from Matsushita et al., 2017 [36]study significantly shifted the SMD from −2.74 [95% CI -3.81 to −1.61] to −5.39 [95% CI -7.33 to −3.34]. As well as, the CIs of the study done by Hirata et al., 2016 are too broad. The publication bias in studies involved in Bilirubin level assessment showed insignificant bias in liver injury (p value = 0.63), as represented in the funnel plot in Fig. 9. For AD, the included studies in the RA subsection were located outside the funnel region, thus, indicating a high risk of potential bias. The

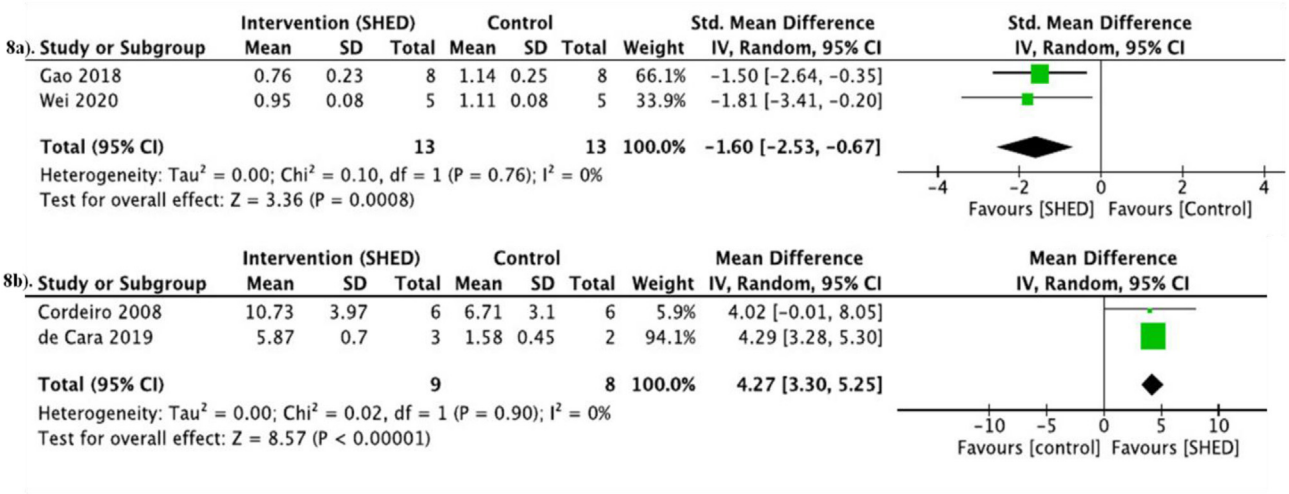


Fig. 8. Forest plot analysis in tooth-related diseases: The diagram represented the pooled effect estimates of SHED treatment in comparison to control in (a) periodontitis and b) Pulpitis.

presence of a study outside the funnel-shaped region in SLE for the assessment of Anti ds-DNA indicated its potential contribution to publication bias [45].

The included studies in wound healing located outside the funnel-shaped region and thus depicted high sensitivity and publication bias (p value = 0.00001). In bone defect sections, studies in calvaria defects contributed to a highly asymmetrical pattern of the funnel plot (p value = 0.06). While in orofacial anomalies, the studies did not exhibit any bias (p value = 0.85). The risk of publication bias in root loss, AD, and post-menopausal osteoporosis could not be accountable as only a single study was available on the respective diseases.

8. Discussion

Stem cells from human exfoliated deciduous teeth unveil mesenchymal stem cell's potential for multi-lineage differentiation, higher proliferative, and doubling capacity and, thus, have been focused on as an alternative approach for adult stem cells in stem-cells based therapy. With the rise in stem cell-based treatment, different types of stem cells and their derivatives are extensively researched and implied in a broad spectrum of diseases. To the best of our knowledge, the current meta-analysis is the first of its kind to evaluate the stem-cell-based therapy approach of SHED in diseases. In the present meta-analysis, out of 2156 published studies, 40 studies are included and reviewed. The included studies target numerous diseases: tooth-related, neurodegenerative, retinal degeneration, liver fibrosis and injury, autoimmune diseases, wound healing and bone defects in orofacial anomalies, post-menopausal osteoporosis, and calvaria defects. Therefore, the pooled effect estimate provides an insight into the statistical significance of SHED intervention. Furthermore, the descriptive analyzed data extracted from included studies showed statistically significant outcomes of SHED intervention.

The forest plot shows that SHED and exosomes were studied in periodontitis and pulpitis models and suggested ameliorating tooth-related ailments. Exosomes, the nanoparticles secreted from donor cells, act as an intracellular shuttling molecule containing various biological molecules and exhibit therapeutic potential for several diseases. In the current study, the subgroup analysis is not feasible, but overall, exosome and SHED enhance bone formation and decrease the ABC-CEJ distances in periodontitis. SHED also improves the formation of microvessels, increases the process of angiogenesis, and statistically enhances the OCN expression in pulpitis and root loss, respectively. Although SHED has shown a beneficial effect in all three aspects (Periodontitis, pulpitis, and root loss), the complete regeneration of the tooth is not achieved as the formation of enamel takes place from ameloblast to be undergone apoptosis after the secretion. In the contemporary tooth-regenerative field, extensive research has been going on to generate whole teeth.

Concurrent with the above-stated meta-analysis, treating MSCs derived from BM, DPSCs, and PDLSCs has increased new bone formation and promoted periodontal and cementum regeneration. An analysis conducted by Novello et al. concluded a small but significant effect on clinical attachment level (CAL) (−0.90 mm, 95% CI [−1.51; −0.29]) after three months of MSCs intervention in humans involving 59 patients with 70 periodontal defects. However, the population's probing depth and gingival recession were not altered significantly [51].

Neurodegenerative diseases and injury cause a considerable burden on wealth and health. The current SHED-based approach investigation in SCI, PD, AD, FCI, and PNI depicted statistically significant pooled effects. Although the test of the overall impact on sciatic excised mice of SCI models is statistically significant, the studies included in SCI showed publication bias while the heterogenicity is moderate. Furthermore, the mode of delivery and the form of SHED in the included studies were similar, while the follow-up period in two studies [21,22] was eight and seven weeks, respectively, and subsequently significantly altered the controls. Concurrent to our investigation, the impending role of MSCs in animal models and clinical trials depicted significant improvement in ASIA motor score, sensory score, and locomotion [52–54]. Similar to SCI, treatment of MSCs in PD, AD, FCI, and PNI illustrated a significantly positive effect. However, AD consists of a single study of SHED intervention; thus, a heterogenicity test is not feasible. A meta-analysis by Ge et al., 2017 indicated improved learning function in AD when treated with bone marrow-derived, human umbilical cord blood-derived, and amniotic MSCs [55].

Furthermore, studies included in PD show similar characteristics and insignificant heterogenicity, thus, removing the need for subgroup analysis. BMMSCs depicted significantly improved rotational behavior in PD [56]. Riecke et al. concluded that MSCs treatment improves rotational behavior and limb function in PD models [57]. In FCI RCTs models, SHED-CM and SHED were administered intranasally and into the striatum, respectively, but didn't suggest any

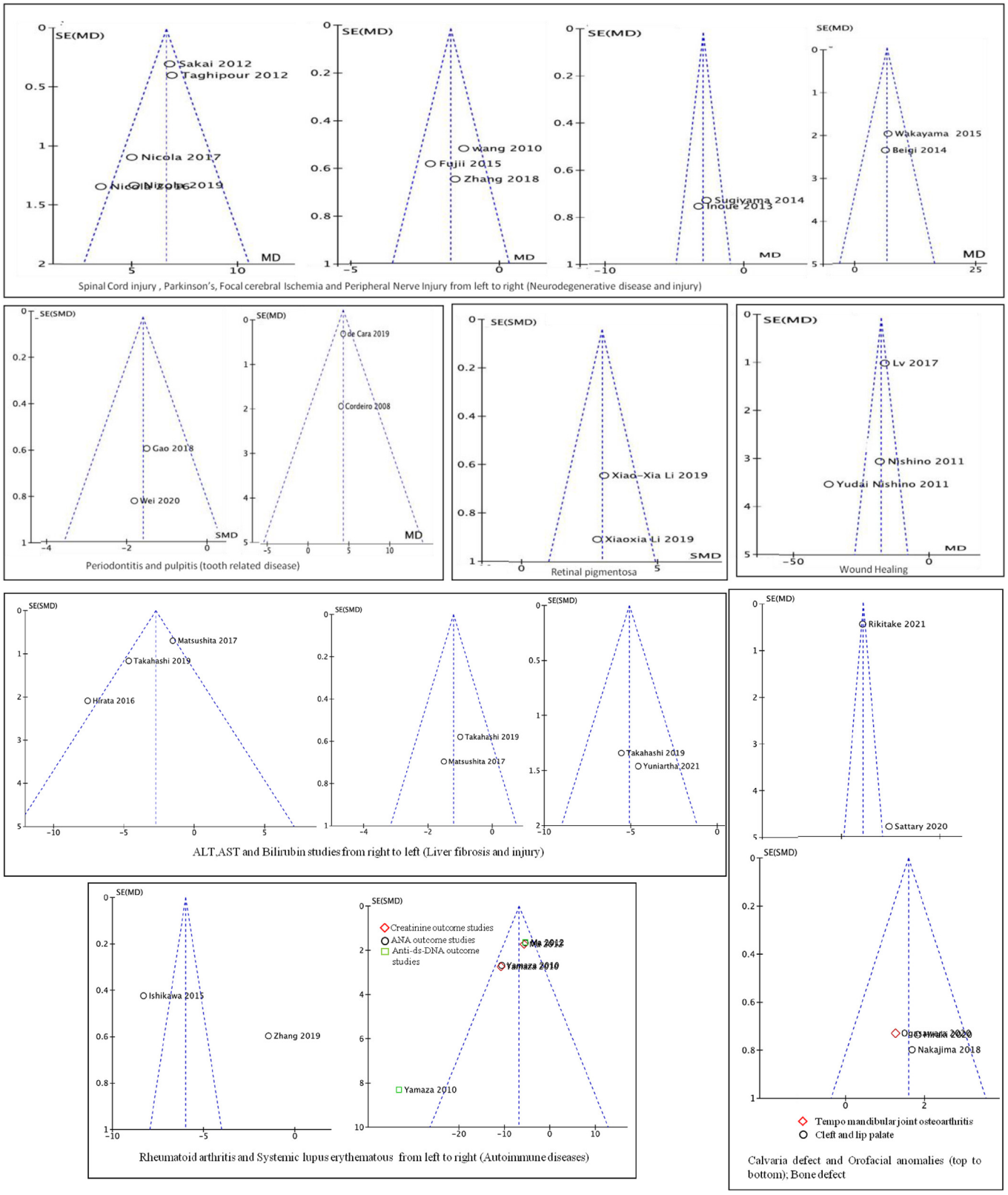


Fig. 9. Sensitivity analysis: Funnel plot analysis of included studies to access publication and sensitivity bias.

significant differences between the mode and form of SHED. The implantation of the SHED-scaffold and SHED-treated nerve guide in PNI show considerable variation between the intervention and the suggested scaffold further enhance the effectiveness of SHED. MSCs regulated the trauma-induced injury microenvironment in PNI via differentiating into neural cells [58].

Analogous to our results, mesenchymal stem-cell therapy reduces wound healing and improves the closure rate [59]. Apart

from MSCs, MSC-EV also reduces wound healing in diabetic-induced ulcer animal models [60]. Although SHED depicted significant regenerative ability in retinal degeneration and diabetic-induced wounds, the included studies in respective diseases have a high risk of publication bias as the included studies correspond to the same author.

MSCs reduce proteinuria levels in SLE with respect to the control group at three months and six months of follow-up [61]. Also, MSCs intervention significantly suspended disease progression and ameliorated experimental autoimmune encephalomyelitis animal models [62]. The results of the current meta-analysis are concurrent and indicate statistically significant benefits of SHED in RA and SLE, but the included studies in RA also show 99% heterogenicity. Therefore, additional studies need to be conducted to draw a conclusive remark on the applications of SHED. The administration of SHED-CM in RA models shows improvement in disease severity score capability compared to SHED. In SLE models, the levels of ANA and creatinine decrease significantly, but the decreases in anti-ds-DNA levels are not statistically significant.

The therapeutic effect of MSCs is broadly developed and researched in bone defects. Studies have concluded the ameliorative impact of different types of MSC in new bone formation, enhanced bone mineral density, and increased bone-to-tissue volume percentage in various bone defects in knee cartilage, alveolar, and mandibular [63–66]. Similarly, SHED depicted improvement in new bone formation and bone-to-tissue volume percentage in our results. The subgroup analysis in Orofacial anomalies revealed that the included studies are not heterogeneous. The included studies consist of SHED and scaffold intervention, but the role of scaffold can't be ascertained as a negative control of scaffold was not taken in one study.

Although included studies demonstrated a statistically high risk of heterogenicity, most of the included studies revealed statistically significant improvement in treating diseases. As the publication frequency of desired findings is more than the non-desired results, the risk of publication bias remains in analyzing the data. Also, the relative number of included studies is low; thus, the potential risk of publication bias is unreliable. The present research majorly focused on investigating and providing an elaborative description of the therapeutic potential of SHED to complete a step towards understanding their role in regenerative medicine. However, the author also tried to accomplish sub-group analysis for a dose of intervention, site of intervention, the effect of scaffolds, effect of type of animal models, but due to the low number of studies further, the efficacy of SHED needs to be thoroughly examined and validated. Our meta-analysis concluded that SHED could be a promising clinical research treatment. Not a single study has deduced and conducted a meta-analysis on SHED in any diseases, but clinical trials are going on SHED in diabetes, liver fibrosis, and pulp necrosis, as illustrated in Supplementary Table 2. Despite the tremendous efficacy of stem cells in preclinical and clinical trials, several key issues need to be contemplated to ensure the safety and effectiveness of the mesenchymal stem cell-based approach in treating diseases. The key factors playing a crucial role in clinical significance are cell source, graft versus host rejection, in-vitro culturing and maintenance, dose, time and route of intervention, and ethical issues. Currently, the clinical application of stem cells poses challenges, and there is a lack of unified principles. Many preclinical and clinical trials are needed to overcome the gap between diagnosis, laboratories, and clinical trials.

8.1. Limitations

In the current scenario, the measure limitations in conducting meta-analysis are (1) few number of published studies; (2) The variation of outcome measures between the studies; (3) The variation in the scale of outcome measure; (4) Lack of brief description of the risk of bias domains by the authors; (4) Short-duration of follow-up after intervention; (5) Diversity of animal types; (6) mode and delivery route of intervention; (7) dose and frequency of intervention and (8) availability of incomplete data or erroneous data; (9) Incomplete data regarding co-morbidities, adverse events, and complications driven by treatment. Furthermore, in the present study, the authors experienced various pitfalls such as the unclear risk of bias in performance bias (blinding and random outcome assessment) in most of the studies, availability of published studies, the language barrier in published studies, risk of publication bias as the authors of published studies have published two studies in the same field, human studies with low population, low number of studies in respective disease thus, attributing a high risk in accessing sensitivity analysis and publication bias. Despite the limitations mentioned above in conducting the meta-analysis, this statistical analysis will still offer comprehensive insights into the therapeutic effectiveness of SHED prior to advancing to clinical trials. A meta-analysis of SHED stem cells is important because, despite the limitations of the included studies, it can nevertheless offer insightful analysis and supporting data. Despite these drawbacks discussed above, a meta-analysis enables a thorough synthesis of the evidence that is currently accessible. Multiple studies are combined, which improves statistical power and results in a more reliable evaluation of treatment effects. As a result, stem cell scientists and clinicians can better comprehend the therapeutic potential of SHED and determine the course of future research.

9. Conclusion

To the best of our knowledge, the present meta-analysis is the preliminary work in inferring the regenerative potential of SHED intervention for the treatment of SCI, PD, AD, FCI, PNI, liver injury, fibrosis, bone defects, wound healing, autoimmune diseases, periodontitis, pulpitis and in retinal pigmentosa comprising forty studies and 565 mouse models of conditions mentioned above. The result of the meta-analysis indicated the statistically significant improvement in reducing ABC-CEJ distance in periodontitis, formation of microvessels and enhancement in angiogenesis in pulpitis models, formation of new bone, and improvement in BBB score, behavioral test, recognition index, and motor disability scores for neurodegenerative diseases. The SHED also significantly reduces the wound area, disease severity score (RA), ANA, and creatinine levels (SLE). Although, the level of anti-ds-DNA in SLE does not show a statistically significant decrease. The treatment of SHED improves ALT, AST, and bilirubin levels in a mouse model of liver fibrosis. In conclusion, the current data support the efficacy of SHED in various diseases in animal models. Along with those mentioned above, the inherent limitations available in study designs of currently available studies need to be acknowledged, and well-designed descriptive studies is need of an hour to corroborate the findings.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors contributions

PY designed the study, collected, analyzed, interpreted the data, and drafted and edited the manuscript. RV and AB edited the manuscript. RN reviewed and edited the manuscript. RB conceptualized study, analyzed, interpreted the data, collected literature, and edited the manuscript. All authors read and approved the final manuscript and approved it for submission.

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Appendix A. Supplementary data

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