

**Evaluation of Stem Cell Research Published in Stem Cell Research and Therapy Journal in the Last 10 Years: A Review**Doke MT<sup>1</sup>, Sayed NA<sup>2</sup>, Shetty YC<sup>3</sup>, Kulkarni A<sup>4</sup><sup>1</sup>Junior Resident, Department of Pharmacology & Therapeutics, Seth G S Medical College & KEM Hospital, Parel, Mumbai 400012<sup>2</sup>Senior Resident, Department of Pharmacology & Therapeutics, Seth G S Medical College & KEM Hospital, Parel, Mumbai 400012<sup>3</sup>Associate Professor, Department of Pharmacology & Therapeutics, Seth G S Medical College & KEM Hospital, Parel, Mumbai 400012<sup>4</sup>Senior Resident, Department of Pharmacology & Therapeutics, Seth G S Medical College & KEM Hospital, Parel, Mumbai 400012

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**Abstract:****Background:** Stem cell research needs to be studied to understand the premise of research and its latest developments. As there was no literature, it was of interest to find out in the last 10 years the stem cell research articles published.**Methods:** After exemption from the ethics committee (EC), a stem cell research and therapy journal site was selected and the search term used was "all articles" and volumes from (1/01/2011 to 1/01/2021) were downloaded. Only original research articles were selected and analysed. The variables used were the source of stem cells, therapy area, category of research, indication, type of research (preclinical/clinical), country of research/Institute/Stem cell research committee approval or EC approval mentioned or not. The variables were analysed using descriptive statistics using SPSS 26 software.**Results:** The total number of original articles analysed was 1846/2476. The most common source of stem cells was Bone marrow. Musculoskeletal therapy was the most common therapy area. The majority of the studies were preclinical. Adult stem cells are the most common cell line used. Institutes in China and the USA are commonly doing studies and the majority were collaborative. Stem cell research committee approval is not mentioned in any of the articles but EC approval is mentioned in all clinical studies. Institutional Animal Ethics Committee (IAEC) approval was mentioned in all preclinical studies.**Conclusion:** Developed countries are at the forefront doing the majority of stem cell research which is preclinical and the common area is musculoskeletal.**Keywords:** stem cell therapy, regenerative medicine, adult stem cell, embryonic stem cell, osteoarthritis.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

There are many chronic disorders without any therapy. So, researchers are searching for new avenues and mechanisms for treating the same. One of the therapies that recently has been explored is stem cell therapy. There are great expectations from stem cell therapy. It was explored and found to be relevant for present times.

The genesis of stem cells is followed from laboratory to controlled stem cell culturing and derivation. There are lot of challenges that stem cell research and therapy need to overcome to be accepted worldwide. A wide variety of possibilities makes this cutting-edge therapy a turning point in modern medicine, providing hope for untreatable

diseases. But did it face the brunt and has given the world any solutions? There were many controversies also surrounding stem cell research. So was it a blessing for the patients suffering from incurable diseases or is it still very experimental in its outlook was very interesting to understand. Mesenchymal stem cell (MSC) treatment is one of the potential hopes in stem cell biology.

However many aspects concerning MSC therapy are still undefined. There are issues in validating their origin, isolation, regenerative potential, differentiation capacity, efficacy and long-term adverse effects. All this evidence regarding stem cells needs to be published. There are very specific

dedicated journals publishing stem cell research both preclinical and clinical. [1-2] Stem cell research is new and for many diseases where there is no cure, stem cell therapy can have a crucial role to play. A few examples to mention are Buerger's disease [3] to COVID-19 [4] which has no definitive line of management. But it may be useful in any area of research: Osteoarthritis, Neurodegenerative disease, Cirrhosis, Pancreatitis, Peripheral vascular Disease, Diabetes mellitus, Stroke, Glaucoma, Retinopathy Macular degeneration [5].

As stem cell research is very specialized in its origin and outcome, every country has its guidelines for it. Categorization of research is another domain that may differ in various countries [6]. According to stem cell guidelines, investigators are bound to do research as per the guidelines. Fewer studies have reviewed the type of studies conducted in this area and the success story of the same. Now if you consider Indian regulation regarding new drug trials, New Drug and Clinical Trial Regulation 2019 (NDCTR 2019) have included stem cell research as new drug research [7]. The literature review found one study on stem cell research registered under [www.ctri.nic.in](http://www.ctri.nic.in) from India [8]. So it was of interest to find out in the last 10 years of stem cell publications if there is any hope or is everything hyped. The objective of the study was to analyse the articles published in the last ten years (1st January 2011 to 1st January 2021) in different therapy areas in the Journal of Stem cell research and therapy.

#### **Objective:**

To analyse the articles published in the last ten years (1st January 2011 to 1st January 2021) in different therapy areas in the Journal of Stem Cell Research and Therapy.

#### **Study Methodology:**

The study was initiated after exemption from review from the Ethics committee (EC-OA-33-2021) as this is a data analytic study available in the public domain. All the measures were undertaken to maintain data confidentiality and privacy. The Stem Cell Research and Therapy Journal was selected for review of published articles on stem cells because it is a PubMed-indexed journal and data from the last 10 years was available online.

Several journals were reviewed including the International Journal of Stem Cell Research, Current Stem Cell Research and Therapy, Journal of Stem Cell Research and Therapeutics and Stem Cell Research, all these were journals publishing studies from 2006, but articles were not available on-site in open access mode. This review was focused on the discovery of different stem cells and

the potential research and its contribution to different therapies. The website of the journal <https://stemcellres.biomedcentral.com/articles> was archived. The search term used was "Original research article". All the articles published in the journal Stem Cell Research and Therapy from 1st January 2011 to 1st January 2021 were retrieved. Two authors checked for the authentication and eligibility of the articles as per the set criteria and later analysed them. The set criteria were Original research articles that included only randomized controlled trials, Case-control studies, Cohort studies, Cross-sectional studies and Systematic reviews and meta-analyses. The studies excluded were review articles, Research commentaries, Letters to Editor, and Short communication. (Excluding Original research).

The variables captured from the articles were - type of research (preclinical/clinical), approvals mentioned of Stem cell research committee or IEC, source of stem cell, country of research/Institute, stem cell lines used, category of research and, therapy area of research

The variables were analysed using descriptive statistics using SPSS version 20 for Windows, Version Chicago, SPSS Inc.

#### **Results:**

A total 2476 articles were published in the stem Cell research and Therapy journal. Out of that, 630 were excluded and total of 1846 articles (74.55%) were analysed. Out of the total analysed articles, 1814 are preclinical (98.26%) and 32 are clinical (1.73%). EC approval is mentioned in all articles, while stem cell committee approval is not mentioned in any study. In country-wise distribution, China is the leading country with 765 articles (41.44%) followed by the USA with 471 articles (25.51%). Number of articles from India is 20 (1.08%).

The most common therapy area is musculoskeletal with 441 articles (23.88%) followed by regenerative medicine with 200 articles (10.83%) (Figure no.1). The status of the type of stem cell used is as follows: 1) Adult stem cell was used in 1034 articles (56.01%) 2) Induced pluripotent stem cell was used in 295 articles (15.98%) 3) Perinatal stem cell was used in 295 articles (15.98%) 4) Embryonic stem cell was used in 222 (12.03%) articles (Figure no.2).

The most common source of stem cell is bone marrow which was used in 701 articles (37.97%) followed by 1) adipose tissue in 443 articles (24%) 2) dental pulp in 223 articles (12.03%) 3) Gingival tissue in 166 articles (9%) (Figure no.3). In clinical studies, most common therapy area is cardiovascular with 8/32 articles and China being the leading country with 16/32 articles (Figure no.4

& 5). The most common source of stem cells in clinical studies were adipose tissue used in 8/23 clinical studies and the study design was interventional clinical trial in 16/32 studies (Figures no.6 & 7). Out of 16 interventional clinical trials, different phases were 1) Phase I studies - 4, 2) Phase II studies - 7, 3) Phase I/II studies - 3 & 4) Phase II/III studies – 2 (Figure no.8).

The study tried to assess the trend of stem cell research published in the last ten years in the Journal of Stem cell research and therapy. We found sizeably more of pre-clinical studies, so still stem cell research is in the establishing stage and the challenges are continuing.

In stem cell research from identification, proper isolation of stem cells, and directed differentiation to immunological acceptance, everything is a challenge. Stem cells are unspecialized cells of the human body. They can differentiate into any cell of an organism and have the ability to self-renewal.

Stem cells exist both in embryos and adult cells, so the study found ample adult stem cell usage followed by induced pluripotent stem cells, perinatal stem cells and embryonic stem cells.

Adult stem cells are undifferentiated and found among differentiated cells after development in the whole body. The function of these cells is to enable the healing, growth, and replacement of cells. These cells have a restricted range of differentiation options whereas ESCs are derived from the inner cell mass of the blastocyst, so these cells are pluripotent in nature, so they can eventually differentiate into every cell type in the organism as per the physiological or environmental exposure. The source of stem cells is very important for therapeutics [5]. The study found the commonest source of stem cells was bone marrow trailed by adipose tissue, dental pulp and Gingival tissue. Pluripotent stem cell was commonly used as per the systematic review by Deinsberger J, et al [9-10].

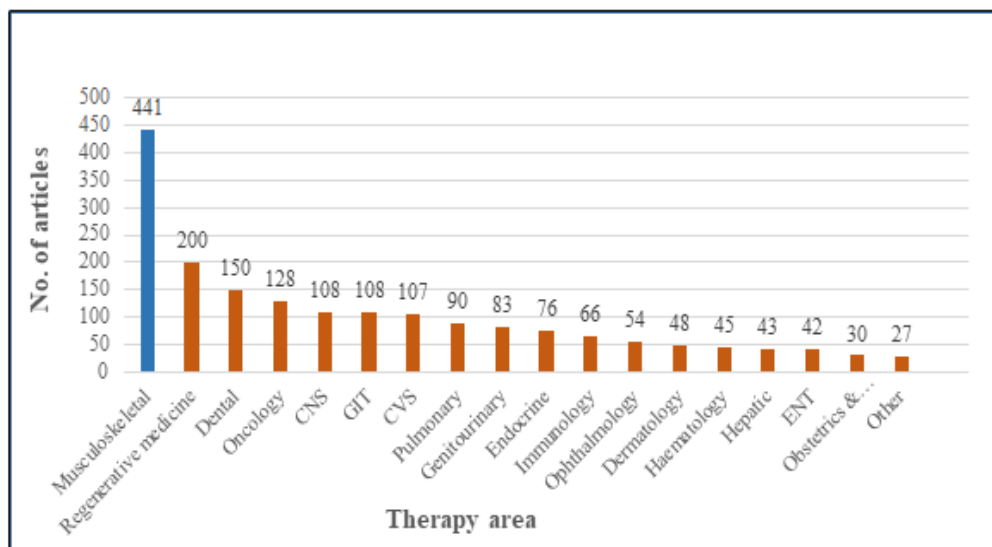
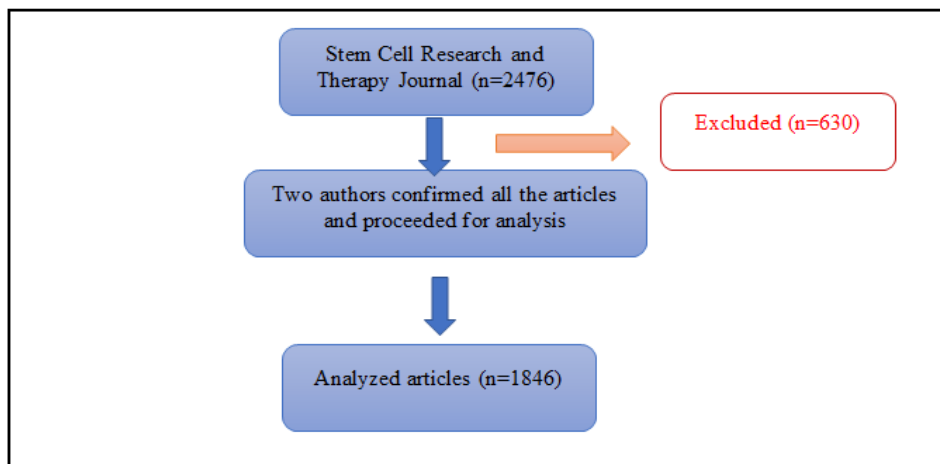


Figure 1: Therapy area (n=1846)

CNS: Central nervous system, GIT: Gastrointestinal tract, CVS: Cardiovascular system, ENT: Ear nose and throat

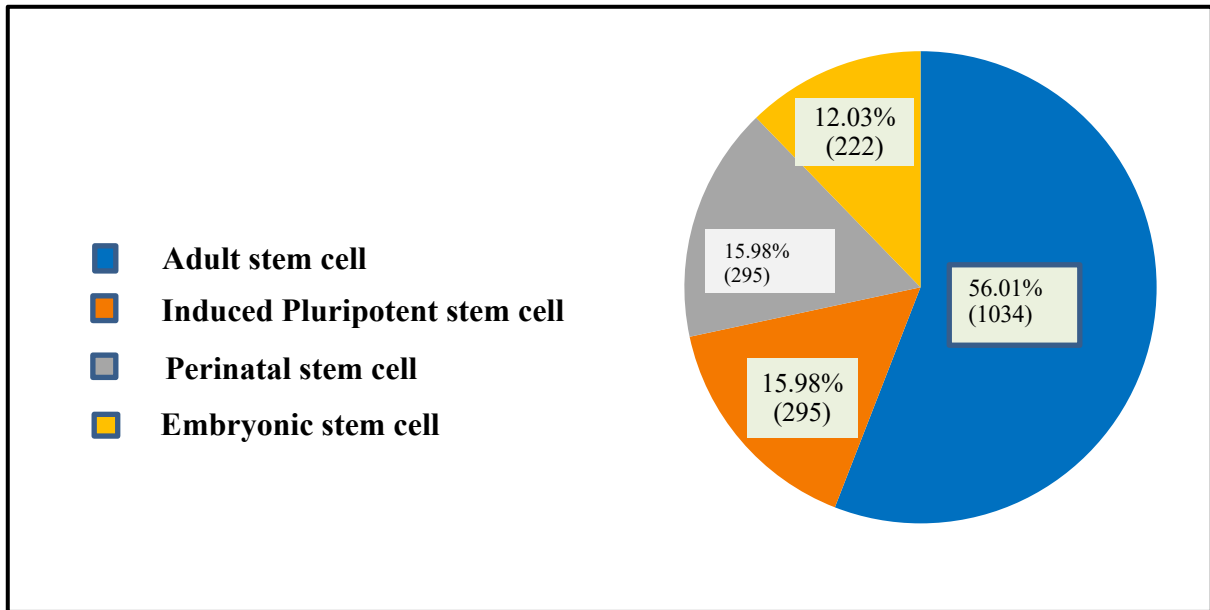


Figure 2: Type of stem cell used in studies (n=1846)

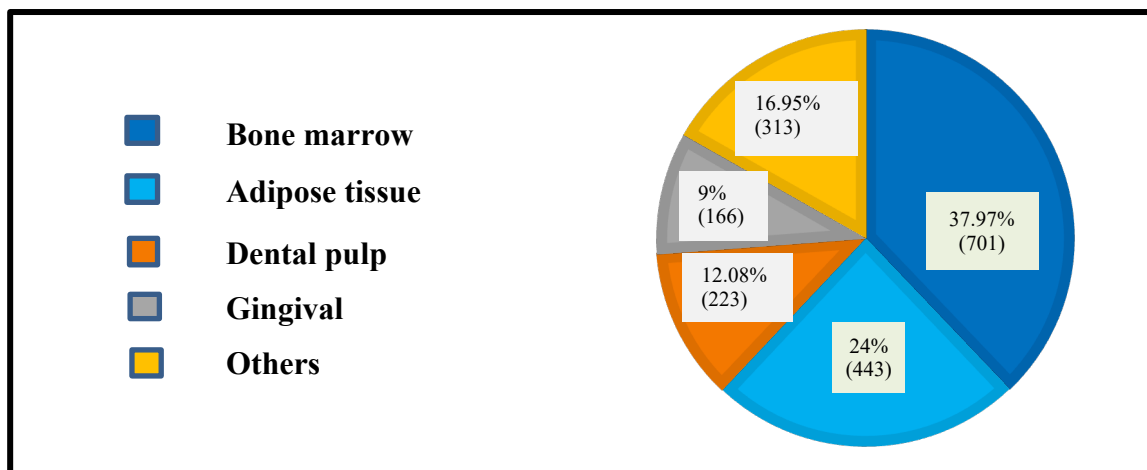


Figure 3: Source of stem cell (n=1846)

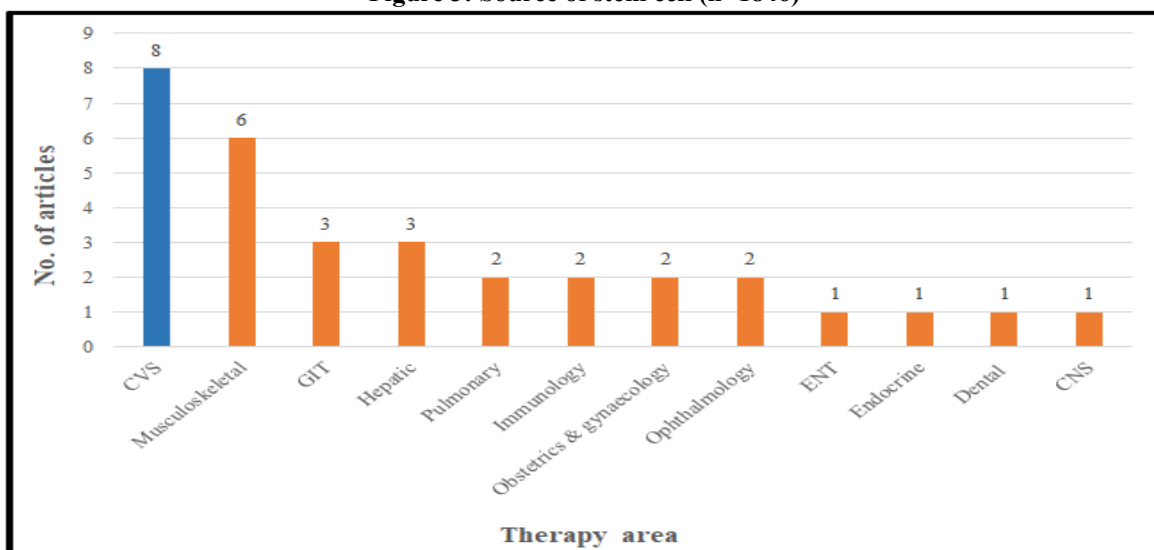


Figure 4: Clinical studies: Therapy area (n=32)

CVS: Cardiovascular system, GIT: Gastrointestinal tract, ENT: Ear, nose & throat, CNS: Central nervous system

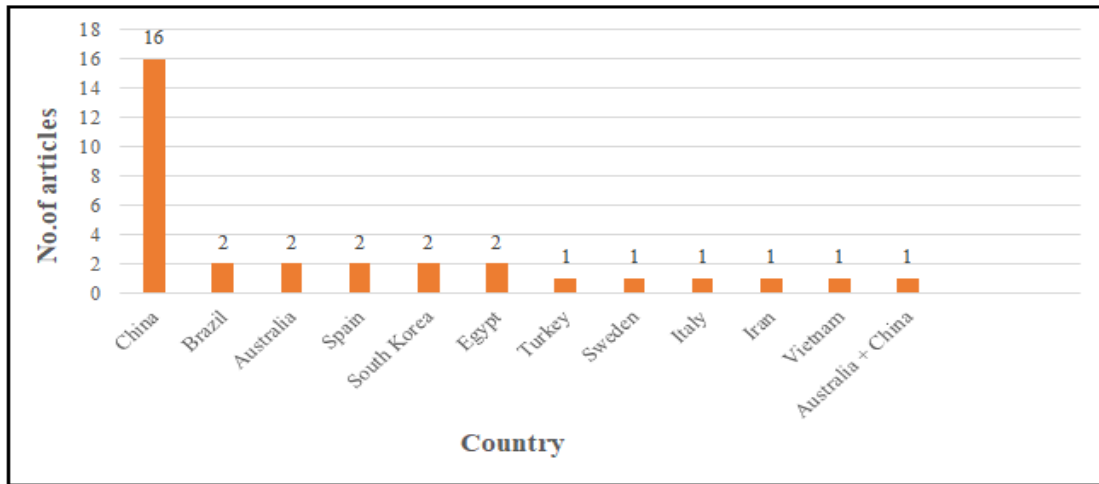


Figure 5: Clinical studies: Country wise distribution (n=32)

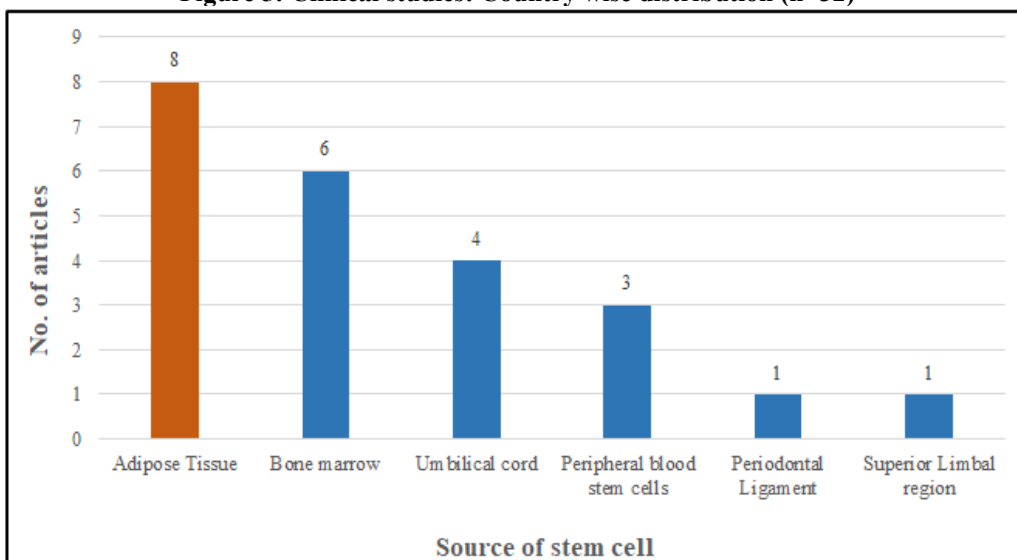


Figure 6: Clinical studies: Source of stem cell (n=23)

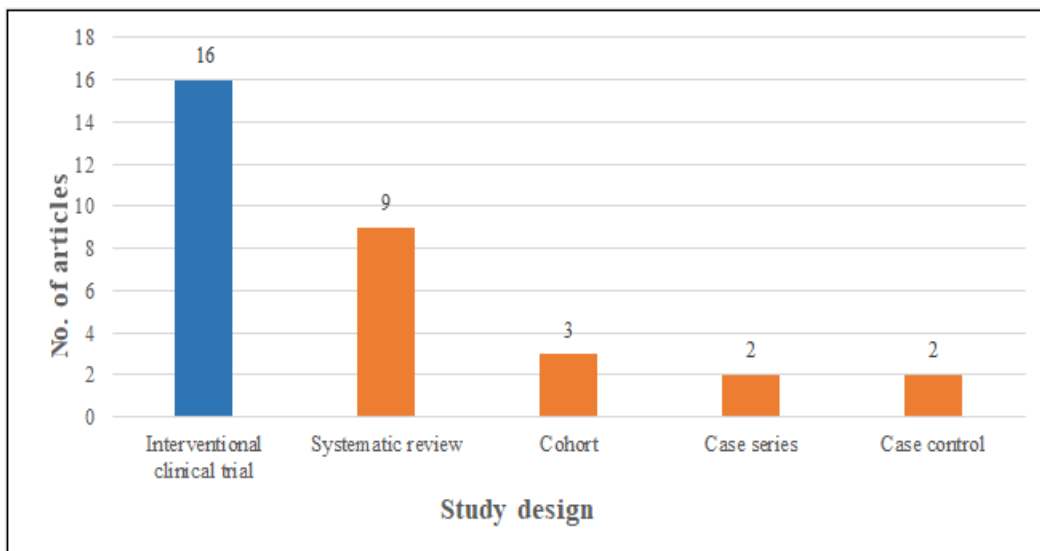


Figure 7: Clinical studies: Study design (n=32)

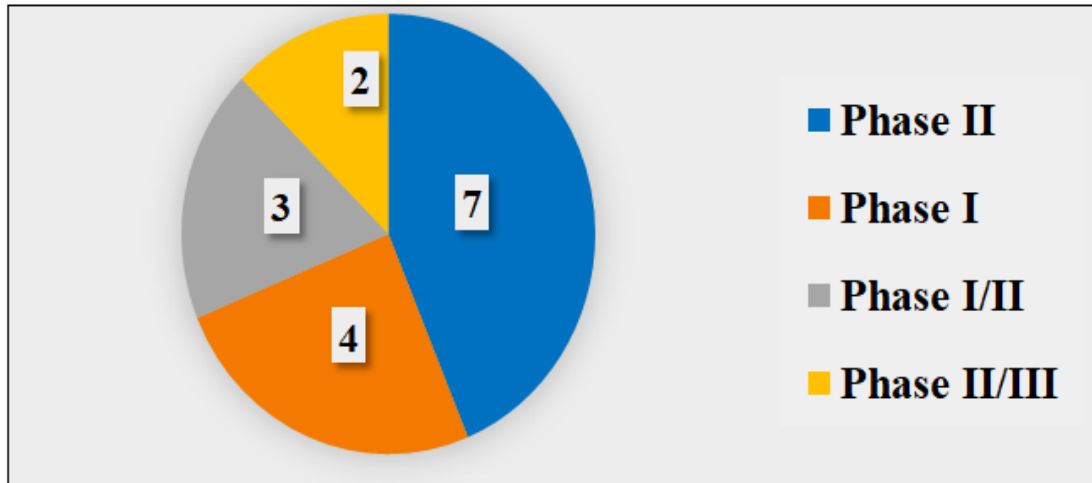


Figure 8: Clinical studies: Type of phase (n=16)

Table 1: Clinical studies: Disease area (n=32)

Phase of study	Area of research	Therapeutic area
Phase I	1. Dental 2. Ophthalmology 3. Musculoskeletal 4. Obstetrics and Gynaecology (OBGY)	1. Periodontitis 2. Retinitis pigmentosa 3. Low back pain 4. Uterine adhesion
Phase II	1. Musculoskeletal 2. Endocrinology 3. Gastrointestinal tract system (GIT) 4. OBGY 5. Pulmonary 6. Central Nervous system (CNS)	1. Knee osteoarthritis 2. Diabetic foot ulcer 3. Crohn’s fistula-in-ano 4. Faecal incontinence 5. Caesarean section skin scars 6. Chronic Obstructive Pulmonary Disease (COPD) 7. Cerebral palsy
Phase I/II	1. Musculoskeletal 2. Ear Nose and Throat (ENT)	1. Osteonecrosis 2. Lumbar degenerative disc disease 3. Vocal fold scar
Phase II/III	1. Cardiovascular system (CVS) 2. Musculoskeletal System	1. Acute myocardial infarction 2. Avascular necrosis of femoral head

**Discussion**

As per the study published by Zakrzewski et al haematopoietic stem cells are the most thoroughly characterized tissue-specific stem cells and studied for more than 50 years [1]. These stem cells appear to provide an accurate paradigm model system to study tissue-specific stem cells, and they have potential in regenerative medicine. Adipose tissue also has its own potential [11], human exfoliated deciduous teeth can be a source of it and it can be of utility in heart muscle regeneration, cardiovascular disease prevention, treatment of spine and orthopaedic conditions and Crohn’s disease [5].

Dental pulp stem cells (DPSC) were the first dental stem cells isolated from the human dental pulp as per Raspini G et al [12]. DPSCs are the most useful dental source of tissue engineering due to their easy surgical accessibility, cryopreservation possibility, increased production of dentin tissues compared to

non-dental stem cells and their anti-inflammatory abilities.

The EC approval is mentioned in all the studies but not the stem cell committee approval. For all stem cell research, there are approvals to be in place, both stem cell approval committee and ethics committee for stem cell studies in humans. If the study is in vivo stem cell research then along with the stem cell committee, approval of the animal ethics committee is mandatory in India. The Department of Biotechnology has released guidelines for stem cell research in India.

The document provides important definitions and elaborates different levels of manipulations; categories of research (permissible, restrictive, or prohibited) and Institutional Committee for Stem Cell Research (ICSCR) and Institutional Ethics Committee (IEC) approval mandatory for non-regulatory studies, but for regulatory studies in



addition Drug controller of India permission is required [6].

Similarly, International Society for Stem Cell Research (ISSCR) has issued guidelines on stem cell research providing contemporary scientific, ethical and policy standards [13]. Even the study could not find stem cell committee approvals in the text but it is understood that the permissions may be in place as per the different journal requirements but ethics committee approval of all the published research was found. China is the leading country doing maximum stem cell research followed by the USA. Deinsberger J, et al in their systematic multi-database analysis of global trends in clinical trials involving pluripotent stem cells found very few interventional studies as compared to observational studies [9-10].

The interventional studies are done in China and observational studies in the USA. The most common therapy areas found were musculoskeletal disease, regenerative medicine, dental indications, oncology, Central nervous system, Gastrointestinal and Cardiovascular diseases.

The study by Larijani B et al has found that cell therapy can be used in the treatment of Parkinson's disease, Amyotrophic lateral sclerosis, Alzheimer's, Stroke, Spinal Cord Injury, Multiple Sclerosis, Radiation Intestinal Injury, Inflammatory Bowel Disease, Liver Disease, Duchenne Muscular Dystrophy, Diabetes, Heart Disease, Bone Disease, Renal Disease, Chronic Wounds, Graft-Versus-Host Disease, Sepsis and Respiratory diseases[5]. As per Rao et al study, studies in Phase 1 and Phase 2 are 49% and 24% respectively[8], while in our study, phase 1 studies were 25% and Phase 2 were 44% so the clinical studies are in preliminary stages from first in human study to exploratory in nature. There are only 2 studies in the confirmatory phase.

The entire research published from 1st January 2011 to 1st January 2021 had very few clinical studies and confirmatory are only 2 studies. The most common therapy area in Rao's study was musculoskeletal followed by cardiovascular and in our study most common therapy area is cardiovascular followed by musculoskeletal area.

**Limitations:** Selection bias cannot be ruled out because it is a single journal-based study.

Stem cell approval may be an inherent part of the publication process, but not found in publication.

### Conclusion

Developed countries are at the forefront doing the majority of stem cell research which is preclinical and the common area is musculoskeletal.

**Implication:** The review will provide data regarding the type of stem cell used, guidelines

followed, type of research and area of research in a nutshell in the last 10 years

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