

**Systematic Review****Ethical Issues and Use of Animal Models in Dentistry - A Systematic Review****Saad Liaqat<sup>1\*</sup>, Sahar Jamal<sup>1</sup>, Saira Ahmad<sup>1</sup>, Fatima Sajjad<sup>1</sup>, Talha Falak Khalil<sup>1</sup>, Humaira Jabeen<sup>1</sup>, Muhammad Adnan Khan<sup>1</sup>, Nawshad Muhammad<sup>1</sup>**<sup>1</sup>Department of Dental Materials, Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, Pakistan**ARTICLE INFO****Key Words:**

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**ABSTRACT**

Prior to conducting therapeutic trials on people, it is critical to do experimental studies on animal models to determine the origin and pathophysiology of the illness process. **Objective:** The objective of this systematic review was to outline the ethical issues involved in the need of animal studies in dentistry. **Methods:** This research was conducted using latest Prisma guidelines 2020. Data retrieved for this study was searched on PubMed, google scholar, and Cochrane libraries. **Results:** Safe and valid experimentation is the key for successful research. In health sector, the precision, accuracy, and validation of the experiment is very critical. It has been a common practice in health sector, that medicine and other surgical research is tested and validated on non-human primates. Once these tests on non-human subjects are replicated and validated multiple times, then the trials on human volunteers are initiated. However, over the years, researchers and different groups have raised serious questions about the abuse of animal studies. Moreover, the technology has progressed quite rapidly. **Conclusions:** The contemporary world is currently dealing with artificial intelligence, virtual reality, and augmented reality. The dentistry is also strong pillar of health services and is not alien to these issues. The outcome of this review is to explore the possibilities of using technology as an alternative to animal in dentistry.

**INTRODUCTION**

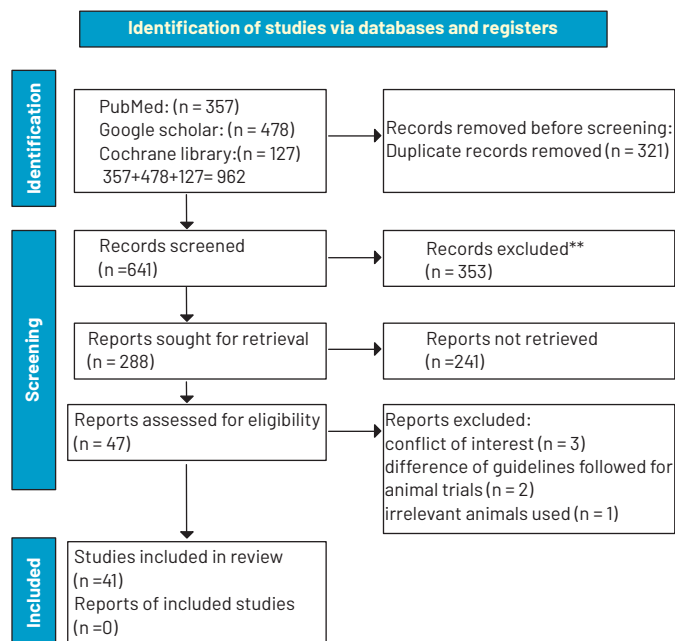
Prior to conducting therapeutic trials on people, it is critical to do experimental studies on animal models to determine the origin and pathophysiology of the illness process [1]. Animal models are thus utilised to analyse the etiopathogenesis, clinical features, immunological and histopathological characteristics of the diseases affecting the periodontium and by testing the success of emerging operational procedures of dental diseases, and to validate the findings before implementation on people [2]. The disorders that affect the gingiva and periodontium are a group of chronic inflammatory diseases that affect the periodontium's supporting tissues. Most importantly, the

bacterial plaque, which is a thin adherent microbial biofilm around the teeth is the primary cause of many periodontal disorders. To prevent these disorders, it's crucial to understand the disease's aetiology, pathophysiology, biomaterial use, and tissue reactions to novel procedures in animal models before applying them to humans.

**METHODS**

This research was conducted using latest Prisma guidelines 2020.

**Search Strategy:** Data retrieved for this study was searched on PubMed, google scholar, and Cochrane libraries (Figure 1).



**Figure 1:** PRISMA flow diagram for inclusion and exclusion of articles

## RESULTS

Different Models in Practice: Primates other than humans, rodents, and other animals such as dogs and hamsters are also employed in dental research, each with their own set of benefits and drawbacks. Various areas of dentistry have used the bulk of animals for the purpose of experiment for last two decades [3]. Most of the animals utilized in dental research were yet alone for the purpose of instructions and training. Smaller animals were mostly used in dental research faculties and larger animals were used as a last resort for testing new surgical methods before they were used on humans. To understand the causes and pathophysiology of periodontal diseases, experiments are done on animals for the purpose of dental research [4]. The use of animal models helped tremendously in the field of tissue engineering. A recent study conducted on rats and rabbits in the year of 2019, has shown the repair of damaged cartilage with the help of mesenchymal stem cells growth through differentiation and replacement of cells [5]. These animals were treated with exosomes which are basically the type of extracellular vesicles that contains proteins, DNA and RNA of the cells that secretes them. Thus, showing increase proliferation of cells and deposition of matrix for the regeneration of cartilage [6]. Various types of animal models were utilised in periodontal research according to the clinical studies and systematic reviews [7]. Benefits of Animal in Research: The following are some of the advantages of using animal models in research.

- The use of animals in study has aided our

understanding of biological processes significantly [8].

- Many significant biomedical breakthroughs have been made as a result of it [9].

- Antibiotics, insulin, vaccinations, and organ transplantation are just a few of the therapeutic and preventative treatments that have been developed using it [10].

**General Practicing Guidelines:** The amended guidelines for the use of animals in scientific study were prepared by the Indian national science academy. It is simple to obey the ethical criteria when it comes to the use of animals in research if you understand the guidelines [11].

- Allowing and providing facilities for the use of animal models for research purposes should be allowed and provided depending on the need [12].

- It is recommended to researchers that they avoid using animals unless it is necessary. They should also make certain that no unneeded strain or injury occurs [13].

- It should offer proper care and housing for the animal models utilized in research, as well as to ensure their physical comfort and their healthy life [14].

- Experiments on animals should be obtained from a well-known animal institution that can provide information on the health, genetics, and status of nutrition of each animal model [15].

- To train and give opportunities to the medical researchers as well as to support the employees who care for them [16].

**Ethical Guidelines:** Before beginning their research with experimental animal models, scientists should follow the rules of ethics towards animals at the level of institution and at the level of national. The animal ethics committee should be rigorously followed by everyone [17]. The committee should include a mix of stakeholders from main research institute, collaborative institute, veterinary specialist, society representative, a member of regulatory agency, and a competent professional in case expected radioactive exposure [18]. Before beginning the experiment, this committee should examine the animals, scientists, and workers managing the animals. The following are some of the ethical rules for using models of animals in dental research that must be followed.

1. Animal research should only be undertaken if they are at utmost importance to improve human or animal health and increasing knowledge in health promotion [19].
2. Ensure that minimum number of animal subjects are chosen.
3. Treat animals with respect and ensure that they have suitable living conditions [20].
4. Anaesthesia should be used for experiments that produce discomfort or pain.

5. Animals that are unable to be alleviated or healed at the conclusion of the study should be put to sleep.
6. Every person conducting animal research should be qualified or have prior experience.
7. Wherever possible, in vitro procedures and ex vivo animal models can be employed to limit the number of animals needed [21].
8. The three r's are the most important rules to follow while conducting research on experimental animal models. Russel and Burch's three r's are replacement, reduction, and refinement. When it comes to experimental animals used in research, the three rules should be followed: the animals should only be used when absolutely required. The sample size for the required number of the animals should be optimized to the minimum level [22].
9. Furthermore, the committee for the purpose of control and supervision of experiments on animals (CPCSEA) instilled the 4 r's credo - replacement, reduction, refinement, and rehabilitation of animals used in experiments [23]. The CPCSEA has made it a national policy to include post-experimentation animal rehabilitation as part of the research. The inclusion of the fourth r's to the research field encourages the researcher to take on more responsibilities [24].

#### **Regulations of Animal Testing with Animal Welfare Act:**

The best science comes from the best animal welfare. The status of an animal is referred to as animal welfare; the treatment that an animal receives is referred to as animal care, livestock farming, and fair treatment [25]. Animal welfare has recently been a major consideration when doing animal experiments. Many regulatory organizations are concerned about animal welfare, and as a result, guidelines for adequate animal care and utilisation during research are being developed [26]. Only after pressure from animal rights organizations and the general public did regulating agencies emerge [27]. These regulatory bodies passed legislation governing the treatment and use of laboratory animals. Regulatory agencies both at national and international level has set up different guidelines to oversee the experiments [28]. The ethical requirements should be met and a prior approval from these regulatory agencies is mandatory before initiating any research on animals [29].

#### **Importance of Animal Profiles Prior to Use in Research:**

Each animal and each experiment have its own pre-requisites. The potential animal subjects should be profiled. The profiling might include psychological standards, research requirements, age, breathing pattern, and temperature, but is not limited to these only. In more precise experiments, even the DNA and the living premises of the animals are tested [30].

#### **Procedures to Reduce Unethical Ways of Animals Use in Dental Experimentation:**

To reduce the unethical ways of using animals in experimentation, alternative models have been introduced. This method is useful as it is time efficient, requires less manpower and cost-effective. Stem cell, DNA chips, microfluidics chips, new image technologies are some examples to animal testing alternatives. No doubt that these alternatives will reduce animal use in and experiments.

**Alternatives to Animal Models:** Possibilities other than animal testing comprise of knowledgeable tests utilizing human cells and tissues which is also called as in vitro techniques, up to date computer-modelling techniques also known as in silico models, and studies involving human volunteers. Technological and scientific advancements in the discipline of toxicology and drug development have declined the demand of animal models [31]. Two new techniques have been used for dental pulp-dentin regeneration [32]. One of which is revascularization procedure while the second approach is to graft mesenchymal stem cells into canals after root canal therapy [33]. Similarly, for dentine regeneration the stem cells play a very crucial role [34]. Exploration of nano medicine cover many localities which include transfer of drugs, formation of vaccines, microbicidal, devices for recognition and imaging, implants, highly productive screening programs by operating biotic, nonbiological, bionics or combination materials [35]. Another technique is the use of macromolecular crystallography for exploratory step which focuses on the use of automated robotics and least human interference [36]. The application of Machine Learning to prognosticate the grade of printing specifying the printing process in extrusion-based 3D printing of biological substances. These procedures manifest acceptable printing situation, thus lessen the number of experimentation necessary for testing [37]. Latest progress in optogenetics have mainly concentrated on neuroscience and has recently shown progress in other fields involving stem cell research and regenerative medicine increasing awareness in well-being and illness conditions [38]. Nano electromechanical systems are developing, along with current scientific learning and technological implementations approaching latest experimental practices and offering new diagnostic and molecular interactive applications [39]. Need for nano informatics arises from some utmost challenges faced by nanotechnology, nanomaterial is helpful in sharing of data and give a way to develop methods and devices specific to the nano level [40]. New strategies have been developing after a lot of efforts for HIV-1 treatment and diagnosis, by using micro- and nano-scale technologies, objective is to

cope up with these problems using emerging technologies [41].

**Future Perspectives:** Science and technology have been widely accepted and integrated into the health sector. With rapid advancement, new streams of research have emerged. In the contemporary research domains, the biomedical research is more relevant to the animal studies. Moreover, the genetic and cellular engineering has been at the forefront of root causes and the solutions various human diseases and viruses.

Some objectives and suggestions to follow during the animal model usage are as follow:

- Replacement of the living subjects to computer experiments and simulations.
- By reducing animal use to by adopting in vitro methods or ex vivo methods
- Advancement to current level in biomedical research can improve the animal models.
- Animals' safety during research and experimentation must be a permanent consideration.

## CONCLUSION

Initially research is an abstract idea, which should be properly tested and verified. The non-human subjects have been used for the overs for this validation. However, these experiments are sometime a source of abuse for animals and in some cases very unethical. Different regulators have set up different guidelines but still the idea of experimenting on live animals is broadly criticized. New technologies such as virtual reality, image processing, and augmented reality has emerged, which could be a good alternative and can be more convincing than other experimentation methods.

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