

Significance of animal model research in Homoeopathy

Basic research in Homoeopathy is in exploratory stage with generating scientific plausibility of ultra-dilutions and further understanding the mechanism of their action. The number of preclinical studies (*in vitro* and *in vivo*) has been conducted in the past aimed at evaluating the pharmacological activity and/or efficacy of some homoeopathic remedies under potentially reproducible conditions.^[1] However, the translation of knowledge from preclinical studies to the clinical level has a gap, due to the limitations of *in vivo* diseases' models.^[2] The *in vitro* studies and clinical researches need to be backed by more research done on the *in vivo*/biological/animal models. Such research must include laboratory models that mimic the clinical application of homoeopathic substances and facilitate research regarding the central issues of Homoeopathy.^[3] HomBRex is a valuable resource and has around 1300 basic research experiments in Homoeopathy indexed so far. It includes research on effects of homoeopathic preparations in bioassays and physicochemical effects of the homoeopathic preparations' process (potentization).^[3]

The organism used as "model" in fundamental homoeopathic research includes animal, human, plant, fungi, and microbial organisms.^[4] Intact organisms or parts of organisms (organs, cells, and subcellular structures) have mostly been used in such basic research. Two major distinctions between human homoeopathic trials and basic studies with cells and enzymes are the placebo effect and the doctor-patient interaction effect. Experimental studies in cell culture and enzymes have many pitfalls but do not include psychological factors.^[4]

ANIMALS IN BIOMEDICAL RESEARCH

The use of animals in research is essential to the development of new and more effective methods for diagnosing and treating diseases that affect both humans and animals. Animals make good research subjects as they are biologically similar to humans. Chimpanzees share more than 99% of DNA with humans, and mice share more than 98% DNA with humans; therefore, animals are susceptible to many of the same health problems as humans thus can be used as experimental models for the study of disease processes. Another major benefit is very rapid turnover rate of the animals, the process of birth to death in a very short timeframe relative to that of humans, and thus, they can be studied throughout their whole life span or across several generations. In addition, scientists can easily control the environment around animals (diet, temperature, and lighting), which would be difficult to do with humans. It is estimated that between 17 and 23 million animals are used in biomedical research each year. Approximately 95% of these are rats and mice specifically bred for research and 4.25% of these animals include rabbits, guinea pigs, sheep, fish, frogs,

insects, and other species.^[5] The use of animals in biomedical research does not only benefit humans but also animals since many of the medicines and vaccines developed for humans are now used to treat animals.

Ethical Context

Most existing animal research policy around the world is concerned with animal welfare and is underpinned by the notion of "the 3Rs:" replacement, reduction, and refinement. Replacement refers to the idea that, wherever possible, the use of animals should be replaced with other methods that do not employ sentient creatures. Reduction concerns the decreasing of the numbers of animals needed in experiments and procedures to obtain meaningful results. Refinement refers to the way experiments are carried out, to make sure that animals suffer as little as possible.^[6] The Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines, were developed as part of an NC3Rs initiative to improve the design, analysis and reporting of research using animals – maximizing information published and minimizing unnecessary studies.^[7] The ARRIVE guidelines have been widely adopted by academic journals to improve transparency and quality in the reporting of research involving animals. A completed checklist can be provided as supplementary information and will help reviewers and editors ensure the high-quality reporting of animal research, compliance with the 3Rs – a description of the relevant ethical approval.^[8] Given that animal research is ethically well grounded and is not abusive, biomedical research is a more meaningful use of animals than their alternative uses as pets, food, transport, or articles of clothing.^[9]

Animal Models

Animal models allow closer approximation to a human response. Some animals are good human-like models for one thing and some for another; some have a cardiovascular system that is similar to humans while others have similar skin. Current examples of animal research in medicine are Alzheimer's disease in mice; tuberculosis in mice and guinea pigs; addiction in monkeys; blood thinners in rats, rabbits, and monkeys; high cholesterol in mice, rats, rabbits, dogs, and monkeys; influenza, swine flu in mice; Parkinson's disease in macaque monkeys.^[10] Most of Homoeopathy studies have been concerned with investigating the interactions between the animal, the disease processes, and the potentized remedies, with the hope that this may be further an understanding of the mechanism of action of homoeopathic remedies.^[11] It is thus vital that researchers are clear about the precise reason for their research and that this is made explicit in publications. Several models used in conventional medicine are required to be validated in homoeopathic research.

RODENT RESEARCH IN HOMOEOPATHY

Rats are most commonly used animal, featuring in 67 experiments indexed in HomBRex. The intact rat is frequently studied to elucidate therapeutic effects of diluted and potentized substances. Most information has been collected with rats in state of induced disease, particularly intoxication, edema/inflammation, behavioral, and hormonal disturbances.^[12] Systematic review of the animal models used in studies of high dilutions covering last decade has yielded evidence of some important intrinsic features in studies of high dilution performed in animal models. The methodological quality based on adequacy of reporting, blinding of measurement of outcomes, nature of control, randomization, statistical analysis, and result was found to be generally adequate. It also discussed convergence between results and materia medica which was seen in some studies^[13,14] pointing toward the possibility of systematic study of the similia principle.^[15] Another group in the analysis tested the putative anti-inflammatory effect of *Rhus toxicodendron*^[16] using various experimental models in rats and mice. This illustrates how using various models can hint at the physiopathological mechanisms of high-dilution effects of 6, 12, 30 and 200cH potencies in reducing paw edema induced by carrageenan. Considering the similia principle to understand these results, only the paw edema model shows gross symptomatic mimesis – or similar template – to the materia medica of *Rhus toxicodendron*.^[15]

A search of the literature and the experiments carried out by the authors of a review showed that there were a number of animal models where the effect of homoeopathic dilutions or the principles of homoeopathic medicine have been tested.^[15] *Causticum* is a homoeopathic medicine which when administered in ponderal doses into the hind paw of rats produced an inflammatory reaction with edema formation within the 1st h, showing that *Causticum* acts as an edematogenic agent. Carrageenan-induced rat paw edema was significantly inhibited in rats treated with *Causticum* 6c, 12c, 30c, and 200c dilutions compared to untreated rats.^[17] A recent study investigated whether potentized homoeopathic drugs such as *Cina*, *Santoninum*, and *Podophyllum* can affect the muscle phase of the parasite in mice. The results showed that *Podophyllum*, *Cina* 30, and *Santoninum* 30 reduced the larval population in the studied mice by 68.14%, 84.10%, and 81.20%, respectively, as compared to the untreated control group.^[18] The concept behind understanding the action of homoeopathic medicine is if a medicine is found to have positive action and modulates well-accepted endpoints, compared to appropriate controls, then one has a clue as to the probable mechanism of action as well.^[19]

Although in emerging stage, we have earlier published number of studies conducted on rat model, namely, evaluation of anti-obesity activity of *Fucus vesiculosus*,^[20] antidiabetic effect of *Cephalandra indica* Q,^[21] therapeutic effect of *Syzygium jambolanum* Q on metabolic disorders,^[22] protective effect of *Zincum metallicum* in Parkinson's disease,^[23] analgesic and

central nervous system depressant activities of *Lycopodium clavatum*,^[24] *Solanum nigrum*,^[25] role of homoeopathic mother tinctures in rheumatoid arthritis^[26] and cerebral ischemia.^[27] These could be made possible by interdisciplinary researches with the collaboration of reputed institutes.

The current issue features encouraging experiments conducted on rodents. Preclinical evaluation of anti-arthritis activity of ultra-diluted preparations of capsaicin alkaloids (CP-10), tumor necrosis factor- α , and *Magnesium phosphoricum* was conducted on Wistar rats which concluded that ultra-diluted preparations exhibited definite anti-arthritis activity.^[28] Next experimental study on rats reported the beneficial role of *Mercurius solubilis* in improving memory function and cerebral blood flow using Morris water maze test.^[29] The author suggested possible use of *Mercurius solubilis* as therapeutic agent in dementia. These publications provide pharmacological evidence to the clinical usage of these drugs and reduce the reliability on symptoms alone while prescribing in Homoeopathic practice. Further on rat model, the acute, sub-acute and chronic oral toxicity of different biochemic drugs *Ferrum phosphoricum* 3X, *Ferrum phosphoricum* 6X, *Calcarea phosphoricum* 6X, *Magnesium phosphoricum* 6X was assessed as per the OECD guidelines. The authors corroborate that these mineral-based homoeopathic drugs are safe and produce no toxicity even when administered for longer durations and therefore are safe to be used in any public health program through health workers.

SCOPE AND OPPORTUNITIES

Quality measurements must be included among the experimental conditions. This, however, requires detailed knowledge of organisms and examination of research methods/protocols by specialists in the corresponding fields of research. For future developments, need is to have debate and discussions on methods of basic research and models in homoeopathy and to have systematic replication or confirmation of certain experimental designs which may contribute to understanding of the similia principle.^[4] The biological studies have more significance when they are successfully replicated and no discrepancies in results are noticed. A systematic review has concluded that there is a lack of independent replication of any preclinical research in homoeopathy.^[30]

The road ahead requires replication of good methodological quality *in vivo* studies, by the researchers at institutes, postgraduate colleges, and doctoral level. India, being academically empowered country in Homoeopathy, has a major role to play in conducting such research. It is imperative that existing education infrastructure undergoes strengthening and our students are given elementary foundation of quantum physics, nanomedicine, modern pharmacology, pharmacogenomics, and pharmacokinetics in their undergraduate course. Once the undergraduates are attuned to these subjects, the postgraduates should be encouraged to take up their dissertations under one of

these subjects. The mentorship under physicists/genetic scientists/pharmacological experts as co-guide is desirable. We need to revisit quote in preface of *Materia Medica* by Boericke,^[31] “Homeopathy is essentially not only many-sided but all-sided. The action of all substances, whether articles of diet, beverages, condiments, drugs or poisons their action on the healthy, the sick, animals and plants is investigated. It advocates the ancient saying, ‘*Prove all things; hold fast that which is good that acts universally.*’ Elimination of the useless may gradually take place with the growth of accurate physiological and pathological knowledge.” There is a need to undertake high-quality clinical studies and back them with quality basic research to eliminate the unreliable contents from the homeopathic materia medica to make it more science oriented. Clinical effectiveness supported by animal model research that is conducted prior and post the clinical trials will play an important role in establishing the scientificity of homeopathic medicines in modern terms. Academic journals also have crucial role to play in setting and maintaining ethical and scientific standards because they are the primary vehicles for the dissemination of findings.^[13] Together these in synergy will eventually lead to growth and development of the science. Homeopathic medical colleges should establish high-quality laboratories for contributing in the basic research using ultra-dilutions.

The current issue also features interesting literature review correlating action of diosgenin and homeopathic pathogenesis of *Dioscorea villosa*.^[32] The author illustrates that effect of pathological activity of *Diosgenin* shown in animal as well as in human models has similarity in the internal pathophysiological changes in homeopathic pathogenesis. In another paper, the antioxidant activity of homeopathic mother tinctures of *Syzygium jambolanum*, *Damiana*, *Cinchona officinalis*, *Chelidonium majus*, *Convallaria majalis*, and *Coca* has been analyzed. It has been found that the total phenolic content present in them and their antioxidant activity can be attributed to their clinical application in prevention and management of certain diseases.

A study conducted to characterize *Aurum metallicum*^[33] by dynamic light scattering, zeta potential, field-emission scanning electron microscopy, and energy dispersive X-ray analysis features in this issue. It evaluates biocompatibility/hemocompatibility of *Aurum metallicum* using hemolysis assay.

In addition, a retrospective analysis of thirty treated cases of calcaneal spur and a case report on ulcerative colitis included in the issue will further enrich the clinical experience of the readers.^[34,35]

Raj K. Manchanda

Editor-in-Chief,

E-mail: rkmachanda@gmail.com

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