

Original article

Zebrafish as an evolving model in Homoeopathy: A Scoping Review

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Abstract

Background: The scientific community has used the Zebrafish (*Danio rerio*) model significantly more often which adheres to the 3Rs (replacement, reduction, and refinement) philosophy. Thus, by substituting Zebrafish for mammals in research, it is possible to decrease the use of those animals and address issues with their welfare. This study aims to explore the scope of the Zebrafish model for research in homeopathy. **Methodology:** Data was collected from various databases such as *Scopus*, *Science Direct*, *Web of Science*, *PubMed*, *Research Gate*, and *Google Scholar*, to identify preclinical studies examining the effects of Homoeopathic formulations on the variance of diseases in Zebrafish. The 11 qualified manuscripts were included for analysis after the identified publications were reviewed in accordance with inclusion and exclusion criteria. **Results:** A systematic search of the databases retrieved 11 studies screened for eligibility after duplicates were removed. A total of 11 articles were assessed with a total of 08 meeting the inclusion criteria and included in the scoping review. **Conclusion:** Zebrafish was revealed to be an ideal model for homoeopathic science to investigate various aspects of human ailments such as toxicity, genetics, behavior, and bone diseases. Additionally, researchers can use Zebrafish to discover novel therapies and preventive measures for a range of human ailments.

Keywords: *Danio rerio*, pre-clinical research, homoeopathy, scoping review

Introduction

The fundamental tenet of Homoeopathy is '*Similia similibus curantur*' (Like cures like), that is, a medication that causes disease symptoms in healthy subjects when taken in high doses will have the opposite effect when taken by sick persons in extremely minute doses [1]. Prior to the 20th century, Homoeopathic research was primarily conducted on healthy human volunteers to demonstrate drug symptoms. In patients with diseases, medications were employed to maximize treatment efficacy. Due to the advancement in scientific knowledge on animal testing, Zebrafish has emerged as an effective in vivo model for preclinical research [2]. George Streisinger and colleagues at the University of Oregon first proposed using Zebrafish as a biomedical model, initiating a new domain for Zebrafish in the field of biomedical research [3]. Zebrafish exhibit numerous intrinsic characteristics as a screening model animal, including many testable embryos, and uncomplicated observation of organogenesis using fluorescence and transgenic strains. Additionally, it provides the capacity to see biological processes and offers the researcher visual connections to the dynamics of organ systems [4]. *Brachydanio*, now known as Zebrafish (*Danio rerio*), is a small tropical freshwater fish which have its origin in the Ganges River and its tributaries in Northern India and

abutting countries [5]. The Ganges and Brahmaputra River basins in Bangladesh, India, and Nepal are just the beginning of their extensive geographic expanse on the Indian subcontinent. Inland waters in the United States (California, Connecticut, Florida, and New Mexico), as well as Columbia, South America, are home to a few invasive populations of the species [6]. The evolutionary observation of the brain, circulatory, and digestive systems of fish and humans has revealed similarities in their structure and physiology. Zebrafish (*Danio rerio*) is one such favorable model for testing drugs for their potential to be used in the treatment of human maladies [7]. The scientific community has used the Zebrafish (*Danio rerio*) model significantly more often which adheres to the 3Rs (replacement, reduction, and refinement) philosophy as demanded by numerous national and international regulatory agencies. In addition, compared to other preclinical models, using the Zebrafish model saves time and resources. Thus, by substituting Zebrafish for mammals in research, it is possible to decrease the use of those animals and address issues with their welfare. Zebrafish are additionally utilized as confirmatory models for earlier findings, thus allowing modification of the results [8]. This study has been conducted with the aim to explore the Zebrafish model for research in Homoeopathy.

Methods

Literature search: This review aimed to present a systematic review of articles related to homoeopathy that used Zebrafish as an experimental model. Data was collected from various databases such as *Scopus*, *Science Direct*, *Web of Science*, *PubMed*, *Research Gate*, and *Google Scholar*, to identify preclinical studies examining the effects of Homoeopathic formulations on the variance of diseases in Zebrafish. A total of 11 articles were assessed with a total of 08 meeting the inclusion criteria and included in the scoping review. Several traditional comprehensive search strategies have been tested based on both Medical Subject Headings (MeSH) and on words in the title, abstract, and keywords in *PubMed*. Irrespective of the exact combination of search terms used, the number of references retrieved became very less to conduct this review. Thus, additional search strategies were performed in *Scopus*, *Science Direct*, *Web of Science*, *Research Gate*, and *Google Scholar* with relevant keywords, linked by 'OR' and 'AND'. The search was restricted to animal experiments in Zebrafish and are published in English. In addition, to find potential studies, we manually searched through study references.

Data Extraction: Data was extracted from the existing research manuscripts related to experiments on Zebrafish available in the English language. Two authors independently collected the information from the data and it was crosschecked and reconfirmed by three authors. The data collected consisted of (1) Author and Year (2) Methodology (3) Results (n=132).

Study selection: Inclusion Strategy: an intensive search of preclinical Zebrafish research manuscripts between 2016 and 2022 was done for this review.

Exclusion criteria: 1. Duplicates, 2. Irrelevant, 3. Review, 4. Non-conventional homoeopathic studies, 5. Studies conducted with the use of mother tinctures, 6. Publications in languages other than English.

Results

A systematic search of the databases retrieved 11 studies screened for eligibility after duplicates were removed. A total of 11 articles were assessed with a total of 08 meeting the inclusion criteria and being included in the scoping review (**Fig. 1**). Of the 03 studies that were excluded for being

mother tinctures (non-dynamized) and complex Homoeopathic formulations, only 08 studies were described as fit (Table 1).

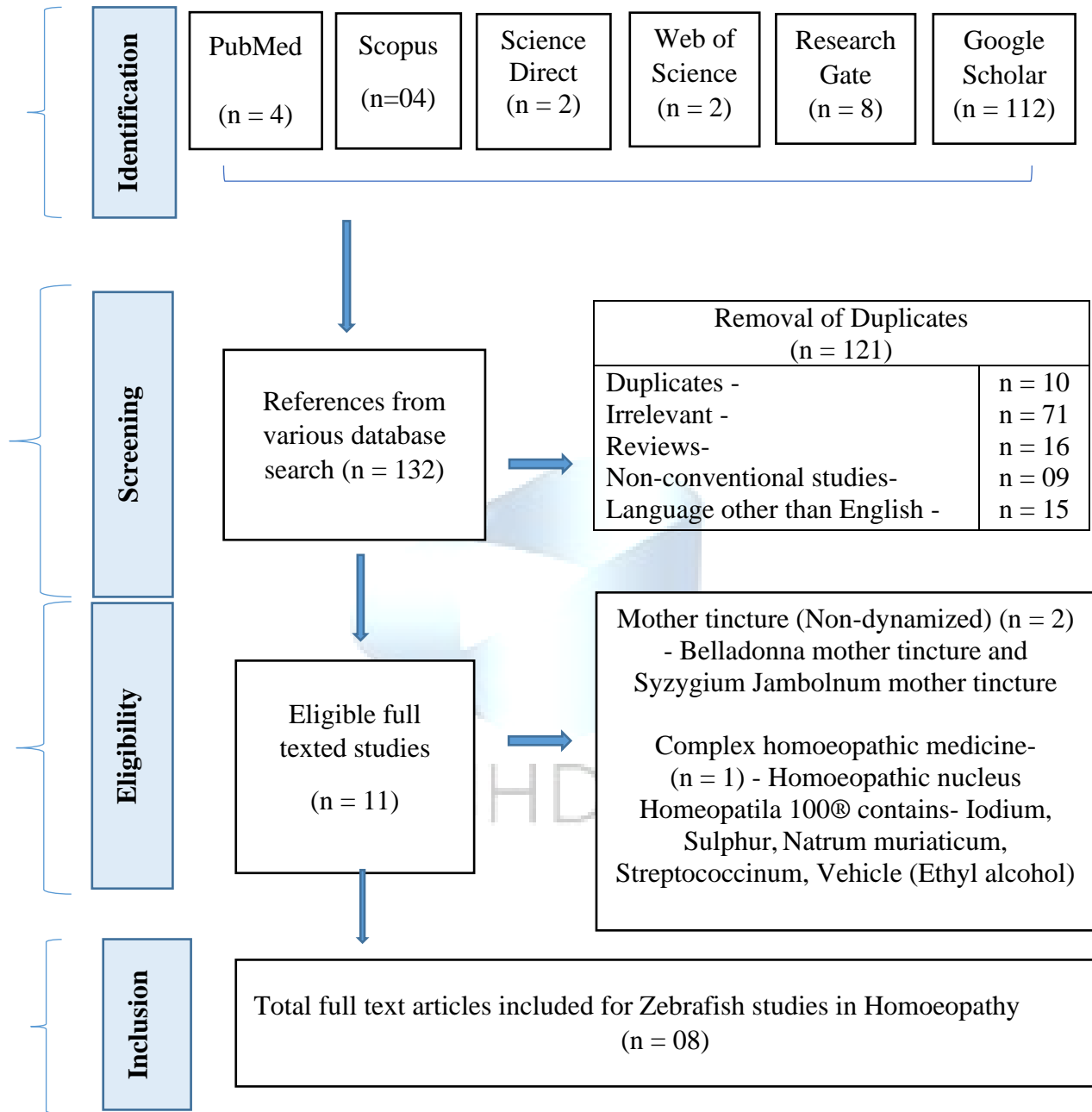


Fig. 1: Inclusion flowchart.

Author (s)	Year of publication	Verum and potency used	Methodology	Results
Velu V, Uthandakal aipandian R [9].	2016	<i>Arsenicum album</i> in 30C and 200C	The acclimatised fish were treated with arsenic trioxide and LC50 was calculated. Along with arsenic trioxide, the homoeopathic medicines were given three drops per liter. After a period of 7 and 14 days, the gills of exposed fish were dissected. The samples were lyophilized and analyzed in Fourier transform infrared spectroscopy.	<i>Arsenicum album</i> 200C was found more effective against Arsenic toxicity. It shows higher dilution may be efficacious to combat this situation.
Himanshu G, Yogesh P, et al [10].	2016	<i>Calcareo carbonica</i> , <i>Argentum nitricum</i> , <i>Sepia</i> in 30C and 200C	Homoeopathic dilutions were investigated using high-resolution transmission electron microscopy and selective region electron diffraction (SAED). Up to five days after conception, Zebrafish embryos were exposed to a test solution between 4 and 6 hours after fertilization, and their viability and morphology were assessed (dpf). Mortality, delayed hatching, phenotypic defects, and metal accumulation were used to gauge the toxicity's effects. It was found that 5 dpf or so was the best developmental stage for evaluation.	The purpose of the current investigation was to unequivocally demonstrate the presence of NPs in all highly diluted homoeopathic medicines. Early in embryogenesis, three homoeopathic medicines in two potencies (30C, 200C) were administered to embryonic zebrafish. Cellular and morphological reactions, as a result, were seen. No pericardial edema, mortality, or visually noticeable abnormalities were caused by exposure to these potencies, also no necrotic or apoptotic cell deaths were found
Ganesh L et al. [11].	2017	<i>Gelsemium</i> and <i>Argentum nitricum</i> in 30C	Adult Zebrafish that were in perfect health were divided into five groups at random, namely control, caffeine-treated, caffeine + <i>Gelsemium</i> 30C, caffeine + <i>Argentum nitricum</i> 30C, caffeine + 0.01% ethanol, and caffeine + buspirone. Fish from each group were let to swim in separate tanks	In a novel tank test, fish treated with <i>Gelsemium</i> 30C showed the least delay, irregular movement, freezing episodes, and length. The CRF and CDK5 gene expressions in both treatment groups with homoeopathic medications significantly decreased, demonstrating their anxiolytic

			containing 0.1% of the respective homoeopathic medications. Following therapy, all groups underwent behavioral analysis in two tests to gauge their level of anxiety: the new tank diving test and the scototaxis test. Studies on the gene expression of CDK5 and CRF were conducted. Elisa technique was used to assess cortisol levels.	properties. Even at their extremely low concentrations, <i>Argentum nitricum</i> and <i>Gelsemium</i> both functioned as potent anxiolytics.
Gupta H and Thakur M [12].	2018	<i>Argentum metallicum</i> , <i>Calcarea carbonica</i> and <i>Sepia</i> in 6C and 30C	Homoeopathic medications were administered to Zebrafish exposed to glucocorticoids for 4, 14, and 28 days at various points, and staining intensities were assessed in comparison to the Control group. Alizarin Red and calcein dye-stained photographs were subjected to appropriate staining intensity measurements.	Zebrafish serve as a useful model for detecting bone abnormalities when homoeopathic medicines are applied to treat osteoporosis.
Coelho C de P et al. [13].	2018	<i>Arsenicum album</i> in 6C and 30C	Zebrafish were divided into four groups of 8 fish each and treated for 96 hours to the heavy metal sodium arsenate before receiving medications prepared from distilled water in the blinded <i>Arsenicum album</i> 6C, 30C, and inert aqueous solution groups. After that, Open Field and the light/dark test (identical anxiety behavior) were assessed for neurotoxic symptoms.	<i>Arsenicum Album</i> , which was more effective as a potential anxiolytic at a concentration of 6C, reduced the anxiety in Zebrafish who had been inebriated by the heavy metal sodium arsenate.
Aiswarya et al. [14].	2020	<i>Sulphur</i> , <i>Arsenicum album</i> and <i>Pyrogenium</i> in 200C	After a month-long acclimatisation period, 15 pairs of healthy aquarium Zebrafish were vaccinated with <i>Vibrio parahaemolyticus</i> . The totality acquired was used to determine how to administer homoeopathic medications. The water from each tank was serially diluted, as well as the fish gut,	Among all remedies, <i>Sulphur</i> 200C showed to be the most effective. Although homoeopathic medications boost a living organism's immunity, they do not create any resistant germs. <i>Sulphur</i> guarantees a complete treatment, meaning that <i>Vibrio</i>

			which was plated in thiosulphate-citrate-bile salts-sucrose (TCBS) agar media. This was done as part of an in vitro study. On Muller Hinton agar media, a growth sensitivity investigation was conducted to demonstrate the growth suppression.	parahaemolyticus is eliminated from the water as well as the fish.
Coelho C de P, et al [15].	2022	<i>Mercurius solubilis</i> 6C, 30C	The fish were divided into 4 monitoring aquariums, each with 8 fish until the commencement of toxicological trials. In each aquarium with six liters of water, 0.5 mL of <i>Mercurius solubilis</i> 6C, 30C, and distilled water (positive control) were added, and the white control aquarium got neither medication nor the lethal agent. Toxic mercury (200 g/L), 4 mL per tank, was added after the medications had been introduced for an hour. This dosage was maintained for 24 hours. The medications were coded and used in an experiment and assessed for neurotoxicity.	Animals exposed to mercury without any form of treatment developed anxiety. The increase in erratic movements (1.25 1.0) and tremors (0.87 0.35) in the vertical open field as compared to the control (0.12 0.35 and 0.25 0.46 respectively) demonstrated the hazardous effect. Fish treated with the drug at 6 C and 30 C exhibited tremors and erratic behavior similar to the control.
Henrique Carvalho Vieira et al [16].	2022	<i>Plumbum metallicum</i> 6cH, 30cH	Before the commencement of the experiment, the <i>Danio rerio</i> fishes were housed in maintenance aquariums with regulated parameters. The experiment was conducted with heavy metal exposure on 8 animals in each of the following groups: white control, medicine at 6cH, 30cH, and inert solution. The animals were then put through anxiety and locomotion tests to determine the animals' neurotoxicity. Since these animals spent less time on the aquarium's bright side and covered less ground there, lead caused anxiety in the fish	The locomotor conditions were reversed in the <i>Plumbum metallicum</i> 6cH group while the neurotoxicological circumstances were reversed in the <i>Plumbum metallicum</i> 30cH group.

			exposed to it. In comparison to the white control group, there was a noticeable reduction in the number of quadrants traversed by the animals that received lead without being exposed to the treatment.	
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Discussion

This review aimed to study the utility of Zebrafish in various diseases for preclinical research in Homoeopathy. To the best of our knowledge, this is the first Zebrafish scoping review in homoeopathy studying Zebrafish as a preclinical model for various diseases. A total of 132 studies were extracted from various databases out of which 11 studies were eligible for analysis from which 08 studies [09-16] were selected according to inclusion criteria and 03 studies were excluded [19-21]. A study was conducted in 2016 to ascertain the efficacy of microdoses' potentized homoeopathic drug, *Arsenicum album* induced by Arsenic trioxide in zebrafish. In this study, the LC 50 values were determined by the method of Sprague. The fish were grouped in triplicate containing 10 fishes in each group and it was divided into Group I-VII. The dose of the Homoeopathic drug was administered by adding three drops per liter of *Arsenicum album* 30C and 200C and was given thrice a day. FTIR technique was used to note the changes in the biochemical contents in gills. The authors concluded that *Arsenicum album* 200C is more effective as compared to *Arsenicum album* 30C. The conclusion of this study indicates that higher potencies are more effective against arsenic poisoning. Furthermore, various potencies such as 1M and 10M should be evaluated for their effectiveness [9]. In 2016, a study was conducted to rapidly assess the toxicity of Homeopathic drugs in an embryonic zebrafish model. The toxic effects of homoeopathic drugs were assessed by observing embryonic mortality, the hatching rate, the presence of malformations, and whole-embryo cellular death. Homoeopathic medicines *Calcarea carbonica*, *Argentum Nitricum*, and *Sepia* in 30C and 200C potencies were used. Toxicity studies were conducted by assembling the fish into six groups to treat homoeopathically. Along with other endpoints, apoptosis in toxicity of homoeopathic medicines was assessed by acridine orange staining. The experimentation result indicates that drugs with 30C and 200C had no toxic effect on Zebrafish larvae and the hatching rates, mortality rate, and morphological development were found to be normal. The authors conclude that the Zebrafish embryo model is effective for testing the toxicity of homoeopathic medicines. This study provides scope for more potentially toxic compound testing in the future [10]. In the 2017 study, the author's direct necessity of functional research on homoeopathic remedies aimed to trace pharmacodynamic action on molecular and genetic levels. Homoeopathic test remedies taken were *Gelsemium serpervirens* 30C and

Argentum nitricum 30C. Adult zebrafish were gathered randomly into six groups each consisting of 10 fish. A diving test and scototaxis test were used to assess anxiety. A gene expression study was conducted for CRF AND CDK5 and cortisol levels were estimated by ELISA test. The experimentation indicated that both the homeopathic remedies showed a sufficient reduction in CRF and CDK5 which indicates anxiolytic potentials even at lower dilutions. The study validates further scope to test various potencies of *Gelsemium serpervirens* and *Argentum nitricum* to confirm its anxiolytic actions [11]. The study was conducted in 2018 to evaluate the homeopathic drugs on Glucocorticoid-Induced Osteoporosis (GIOP) Zebrafish model to investigate secondary osteoporosis and increase bone fragility. The study aimed to determine the role of homeopathy as a complementary treatment to modern science. *Argentum metallicum*, *Calcarea carbonica* and *Sepia* in two dilutions 6C and 30C. Three different exposure points at 4, 14, and 28 days were studied. Image J software was used to measure staining intensities for Alizarin Red and Calcein dye stained images. The statistical analysis showed that GIOP and other treated groups were not significant at $p < 0.05$ for a 28-day study with Calc. carb 30C and Sepia 30C. The authors concluded that Zebrafish is an effective model to study bone defects and pointed out the Calcein staining protocol to be a powerful tool to monitor mineralized structures; this can be base for further studies to test various diluted potencies and more research can be conducted for the Glucocorticoid-Induced Osteoporosis Zebrafish model [12]. A study was conducted in 2018, in Brazil with the aim to assess the neurobehavioural state of *Danio rerio* which was intoxicated with sodium arsenate, and to study the role of *Arsenicum album* to reverse the condition of anxiety. The homeopathic remedy *Arsenicum album* 6C and 30C was prepared according to Brazilian Homeopathic Pharmacopeia using distilled water. The fish were exposed for 96 hours to sodium arsenate and four groups were formed. The assessment was based on time and frequency on the surface, erratic movements, seconds of immobility, and the number of times the fish crossed from a light to a dark compartment. In fish, untreated with medication, sodium arsenate produced an anxiogenic effect. The group with *Arsenicum album* 30C showed a reduction in erratic movement whereas the group treated with *Arsenicum album* 6C reversed all positive control parameters. The authors concluded that the 6C potency of the *Arsenicum album* was more effective as an anxiolytic. Different dilutions of the remedy can be tested using guidelines of different pharmacopoeias [13]. A study was conducted in 2020 with the aim to evaluate the effect of homeopathic medicines on diseases caused in humans due to fish. The Zebrafish model was used for experimentation, for which 15 pairs of 3 weeks old zebrafish were procured. Inoculation of vibrio parahaemolyticus was done by impregnation technique on day 31 dpf. Fish were separated into five groups from A to E and medicines were administered symptomatically. *Sulphur* was found to be most effective with a 0% mortality rate followed by *Arsenicum album* and *Pyrogenum*. *Sulphur* and *Arsenicum album* showed a cure for gastroenteritis in fish [14]. In a study conducted in 2022, authors have aimed to test mercury-induced behavioral changes using the Zebrafish model (*Danio rerio*). The assessment was based on locomotor activity and neurotoxicity parameters to check if ultra-diluted substances decrease neurobehavioral toxicity and effects. The fishes were grouped into 4 monitoring aquariums consisting of 8 fish each, with temperature, and pH controlled, until the time of the toxicological experiments. The medications were coded and used to identify them during the entire experiment. Each step of the behavioral tests—Open Field for locomotion, Vertical Open Field to assess neurotoxicity, and Light and Dark Test—was videotaped for further analysis of the

animals' movements and neurobehavioral alterations. The authors concluded that fish can develop neurobehavioral issues when there is 200 g/L mercury in the water, however, animals given the ultra-diluted drugs *Mercurius* 6C and 30C did not exhibit neurotoxicity [15]. A study was conducted in 2022, authors aimed to test behavioral changes caused due to lead toxicity. Zebrafish (*Danio rerio*) were exposed to heavy metal and treated with *Plumbum Metallicum* 6 cH and 30 cH, the fish were divided into 4 groups consisting of 8 fish in each group. The groups were white control, medication at 6cH, 30cH and inert solution. Animals were then subjected to behavioral tests (such as anxiety and locomotion tests) to determine the level of neurotoxicity. When compared to the white control group, the animals that received lead had a noticeable reduction in the number of quadrants they traversed in the open field. The locomotor conditions were reversed in the *Plumbum metallicum* 6cH group, whereas the neurotoxicological circumstances were reversed in the *Plumbum metallicum* 30cH group. This study provides further scope for the toxicological evaluation of various hazardous metals affecting mankind [16]. Zebrafish proves to be a feasible in vivo model due to its cost-effectiveness, faster maturation rate, transparent body, and its resemblance to humans; for conducting various medical research [17]. One major limitation of the Zebrafish observed was, due to its small size, minute changes were not noticeable compared to other biomedical models [18]. Our current review provides further scope for testing of toxicity of substances in drug development experiments and other human diseases.

Conclusion

Zebrafish was revealed to be an ideal model for homoeopathic science to investigate various aspects of human ailments such as toxicity, genetics, behavior, and bone diseases. Additionally, researchers can use Zebrafish to discover novel therapies and preventive measures for a range of human ailments. With the development in the field of nanotechnology and molecular methods, Zebrafish can be employed as an ideal model in preclinical research in Homoeopathy.

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Conflict of Interests

The authors declare no conflict of interest.

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