ZEBRAFISH AS AN EMERGING IN VIVO MODEL IN DENTOMAXILLOFACIAL RESEARCH

(IKAN ZEBRA SEBAGAI MODEL IN VIVO DALAM PENELITIAN DENTOMAKSILOFASIAL)

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ABSTRACT

Animal models are vital in dental research for studying dentomaxillofacial anomalies, disease mechanisms, and therapeutic strategies. Conventional models, such as those using rodents and higher mammals, provide valuable insights but raise ethical, financial, and translational challenges. Zebrafish (*Danio rerio*), widely established in biomedical sciences, offer distinctive advantages including genetic similarity to humans, transparent embryos, rapid development, and low maintenance costs. Despite their potential, their use in dental research remains relatively limited. This review evaluates current and emerging applications of zebrafish in dentistry based on peer-reviewed literature and institutional resources. Research highlights three main areas. In tooth and craniofacial development, zebrafish contribute insights into odontogenesis, regeneration, and congenital anomalies through continuous tooth replacement and conserved pathways such as bone morphogenetic protein (BMP) and Hedgehog. In dental material studies, zebrafish embryos serve as sensitive models for assessing systemic and craniofacial toxicity of fluorides, nanoparticles, alloys, bioceramics, and resin-based monomers. In oral cancer research, transparent zebrafish lines and xenograft models enable real-time visualisation of tumor progression, metastasis, and treatment response, supporting high-throughput drug screening. Although limitations such as the absence of permanent dentition and anatomical differences restrict direct translation, zebrafish provide a rapid, ethical, and cost-effective complement to mammalian models—advances in genetics and imaging promise to expand their role in dental research and strengthen their translational relevance.

Keywords: animal model; craniofacial development; dental materials; oral cancer; zebrafish.

ABSTRAK

Model hewan sangat penting dalam penelitian gigi untuk mempelajari anomali dentomaxillofacial, mekanisme penyakit, dan strategi terapeutik. Model konvensional seperti hewan pengerat dan mamalia yang lebih tinggi memberikan wawasan berharga tetapi menimbulkan tantangan etika, keuangan, dan translasi. Ikan zebra (Danio rerio), yang mapan luas dalam ilmu biomedis, menawarkan keunggulan khas termasuk kesamaan genetik dengan manusia, embrio transparan, perkembangan yang cepat, dan biaya perawatan yang rendah. Terlepas dari potensinya, penggunaannya dalam penelitian gigi masih relatif terbatas. Tinjauan ini mengevaluasi aplikasi ikan zebra saat ini dan yang muncul dalam kedokteran gigi berdasarkan literatur peer-review dan sumber daya institusional. Penelitian menyoroti tiga bidang utama. Dalam perkembangan gigi dan kraniofasial, ikan zebra menyumbangkan wawasan tentang odontogenesis, regenerasi, dan anomali bawaan melalui penggantian gigi terus menerus dan jalur yang dilestarikan seperti BMP dan Landak. Dalam studi bahan gigi, embrio ikan zebra berfungsi sebagai model sensitif untuk menilai toksisitas sistemik dan kraniofasial fluorida, nanopartikel, paduan, biokeramik, dan monomer berbasis resin. Dalam penelitian kanker mulut, garis ikan *zebra transparan dan model xenograft memungkinkan visualisasi real-time perkembangan tumor, metastasis, dan respons pengobatan, mendukung skrining obat throughput tinggi. Meskipun keterbatasan seperti tidak adanya gigi permanen dan perbedaan anatomi membatasi translasi langsung, ikan zebra memberikan pelengkap yang cepat, etis, dan hemat biaya untuk model mamalia. Kemajuan dalam genetika dan pencitraan menjanjikan untuk memperluas peran mereka dalam penelitian gigi dan memperkuat relevansi translasi mereka.*

***Kata kunci** : dental material; ikan zebra; kanker mulut; model hewan; perkembangan kraniofasial*

INTRODUCTION

The use of animals in research is essential for advancing knowledge in biomedical sciences and for developing new diagnostic and therapeutic approaches. Animals serve as in vivo models for studying various human diseases and their treatments.[1] In drug discovery, animal testing plays a pivotal role in evaluating the safety and efficacy of potential drug candidates before human clinical trials.[2] Many species used for research are bred explicitly in laboratory settings. Over 90% of laboratory animals are rodents, particularly mice and rats. In comparison, a smaller proportion less than 10% includes higher-order species such as dogs, monkeys, rabbits, and pigs, which are used for specialised experiments.[3]

In dental research, animal models are extensively employed to investigate periodontal disease, peri-implant conditions, tooth development, dentomaxillofacial anomalies, oral pathogenesis, and a wide range of oral diseases.[4] The selection of an appropriate animal model is based on either anatomical and physiological analogies or evolutionary homologies to humans. Several factors must be considered when choosing the right animal for a given experiment, including the specific research aims, the nature of the study, animal welfare conditions, cost, and availability.[5]

Animal experimentation has contributed significantly to the development of various pharmaceuticals and medical treatments for human use. Nevertheless, growing ethical concerns about animal testing, particularly regarding the moral justification of using animals for human benefit, have spurred debates in both scientific and public communities. While the benefits of animal research are well documented, increasing awareness of its limitations, including the relevance of animal data to human biology, has prompted critical reassessments.[6] Problems, such as drug development failures due to toxicity or lack of efficacy, coupled with flawed experimental designs. It has led to stricter legislative regulations and the establishment of animal ethics committees to evaluate experimental protocols thoroughly. Additionally, the high costs associated with animal experiments can further constrain their use.[7]

Rigorous guidelines govern animal research to ensure both scientific validity and humane treatment of animals. One of the most influential ethical frameworks in animal research is the 'Three Rs' principle—Reduction, Replacement, and Refinement—which has been widely adopted across many countries as a cornerstone of responsible scientific practice.[6,8] Reduction refers to minimising the number of animals used and avoiding unnecessary duplication of studies. Replacement advocates the use of non-animal alternatives whenever feasible, such as computational models or simulations. Refinement emphasises the design of experimental procedures that minimise pain, distress, and suffering in animal subjects.[8]

In recent years, the zebrafish (*Danio rerio*) has gained prominence as an alternative vertebrate model in biomedical research. Due to its anatomical and functional similarities with key organ systems in humans, the zebrafish presents a viable substitute to reduce the reliance on mammalian models.[9] Zebrafish are genetically well characterised and share considerable genomic homology with humans, making them particularly suitable for studies in genetics, human disease modelling, biomedicine, and biotechnology.[9] In the field of dental research, the use of zebrafish holds several advantages, offering a valuable alternative to mammalian models and potentially reducing unnecessary mammalian experimentation. However, their application in dental and dentomaxillofacial studies has received little attention. This review aims to highlight the potential of zebrafish as a model organism for dentomaxillofacial research.

METHOD

This narrative review draws on information from peer-reviewed articles indexed in Scopus, PubMed, and Google

Scholar over the past decade (2015–2025). The search used a combination of keywords, including 'animal model,' 'craniofacial development,' 'dental materials,' 'oral cancer,' and 'zebrafish'. Additionally, the Zebrafish Information Network (https://zfin.org/) and the official websites of various research and educational institutions were referred to.

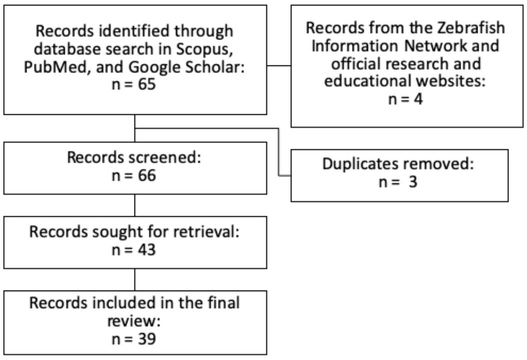

Figure 1. Narrative Review Flow Diagram.

DISCUSSION

Biological Characteristics and Experimental Advantages of Zebrafish

The zebrafish (*Danio rerio*) is a small vertebrate organism native to the freshwater habitats of South Asia. It belongs to the family *Cyprinidae* and thrives in tropical freshwater environments. Adult zebrafish typically measure 1.5–2 cm in length and are easily recognisable by their distinctive horizontal dark- and light-striped patterns. Sexual dimorphism is apparent; males are generally more slender, with a yellowish colouration, whereas females display a larger, more rounded silver body. Females are highly fecund, capable of spawning every 2–3 days, and produce several hundred eggs at a time. The eggs, approximately 0.7 mm in diameter, are transparent and develop characteristic body stripes as the fish matures into adulthood[10,11].

In recent years, zebrafish have gained widespread recognition as model organisms across multiple research disciplines, particularly in genetics and human disease studies. Their popularity is attributed to several advantages, including low-cost husbandry, prolific breeding capacity, and short generation time (Fig. 2). Embryonic development in zebrafish occurs rapidly. It can be visualised within a few days, in contrast to the weeks or months required in mammalian models. The optical transparency of embryos allows researchers to directly observe the brain, heart, gut, and other vital organs at high resolution, facilitating detailed studies of developmental processes and pathological changes.[10] Moreover, researchers can detect morphological defects or malformations as early as the first stages of embryogenesis.

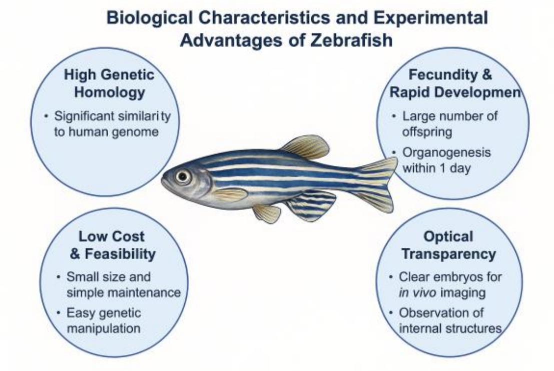

Figure 2. Zebrafish Offer Key Benefits for Research, Including High Genetic Similarity to Humans, Rapid Development and High Fecundity, Optical Transparency for Live Imaging, and Low Maintenance Costs—Making Them a Versatile and Efficient Model Organism.

Zebrafish embryos are self-sustaining in early development, deriving nutrition from their yolk sac for several days without external feeding.[12] Laboratory conditions for rearing adult and juvenile zebrafish typically involve glass aquaria maintained at a temperature of 26 ± 1 °C, with water parameters carefully controlled at pH 6.8–7.2 and hardness of 3–6°dH. A light/dark cycle of 10–12 hours is commonly used to regulate circadian rhythm. Although maintenance of water systems requires careful management, zebrafish adapt well to controlled laboratory environments and have become widely used for experimental research.

Importantly, zebrafish possess well-characterised genetics. The zebrafish genome, sequenced and mapped through initiatives such as the Sanger Institute project (http://www.sanger.ac.uk/Projects/D_rerio/), shows significant homology with the human genome (Fig. 1), supporting their use in large-scale genetic studies, embryonic development research, and modeling of human diseases.[12] Beyond developmental biology, zebrafish have also been utilized as a regenerative model; for example, their larval tail serves as a reproducible system for investigating wound healing and tissue repair responses.[13]

Zebrafish as Animal Models in Tooth and Craniofacial Development

Tooth developmental studies primarily focus on embryogenesis and dentition patterning. The zebrafish (*Danio rerio*), a polyphyodont vertebrate, exhibits lifelong tooth replacement, making it a valuable model for regenerative dental research. In adults, teeth are located on the pharyngeal jaws formed by the ventral fifth ceratobranchial arch, consisting of three rows and a total of 11 teeth: ventral (1V–5V), medio-dorsal (1MD–4MD), and dorsal (1D–2D).[14] Tooth resorption is followed by new tooth formation at approximately the same position, coordinated by an odontogenic wave that ensures each generation is at the same developmental stage. New transverse rows form posteriorly to the older ones.[15] Structurally, zebrafish teeth share key features with mammalian teeth. The crown is composed of dentin, capped with an enameloid layer, and contains a pulp cavity with odontoblasts. However, larval teeth show fewer odontoblasts and lack tubules, while adult teeth possess both innervation and vascularisation.[16] Notably, zebrafish lack cementum due to the absence of permanent teeth. This simplicity allows researchers to dissect core signalling pathways without the confounding complexity found in mammals.[17]

Genetically, zebrafish have proven instrumental in understanding molecular pathways involved in dental development. Bone morphogenetic protein (BMP) signalling is active across nearly all stages of tooth development, guiding morphogenesis and differentiation.[15] Likewise, Hedgehog signalling, particularly via *shha*, is essential; its knockdown impairs proper tooth maturation.[18] Fibroblast growth factor (FGF) pathways are also implicated in the early morphogenetic stages.[19] Beyond teeth, zebrafish are invaluable in the study of craniofacial development. Zebrafish embryos develop transparent tissues, facilitating real-time imaging of craniofacial morphogenesis. Mutational analyses have identified at least 48 mutations across 34 genetic loci affecting craniofacial features.[20] Zebrafish also enable modeling of craniofacial anomalies and neural crest cell dynamics, which are crucial in maxillofacial development.[21] Importantly, zebrafish possess a remarkable regenerative ability, capable of restoring dentin and supporting continuous tooth cycling. Their utility in modeling diseases like osteogenesis imperfecta further underscores their translational relevance in both skeletal and dental research.[22] In summary, zebrafish provide a genetically tractable, ethically manageable, and biologically relevant model for studying the molecular and developmental dynamics of tooth and craniofacial formation. Their increasing adoption in dental science promises refined insights into regenerative biology and congenital anomalies, as outlined in Table 1.

Zebrafish in Dental Materials Research

Zebrafish (*Danio rerio*) embryos have become an established in vivo model for chemical toxicity testing and early phase drug discovery because of their optical transparency, high fecundity, and conserved genetic pathways in humans. They have been used to assess the toxicity profiles of a broad range of compounds, including those affecting cardiotoxicity, neurotoxicity, ototoxicity, seizure activity, and gastrointestinal function.[23] The OECD Fish

Embryo Toxicity (FET) test provides a standardised guideline for evaluating embryonic toxicity in zebrafish and is frequently applied in chemical safety studies, including dental materials research.[24]

In dentistry, various materials—ranging from fluoride agents to restorative and implant components—require toxicological assessment. Zebrafish models have been increasingly utilised to evaluate the systemic toxicity and cytocompatibility of these materials (Table 1). For instance, sodium fluoride (NaF), widely used for caries prevention, has been studied for its toxicological effects in zebrafish. Exposure to NaF resulted in enameloid alterations, increased organic content in the teeth, and visible malformations in primary dentition, resembling features of dental fluorosis.[25] Karaman and Emekli-Alturfan also emphasised the importance of zebrafish in assessing fluoride toxicity at the molecular and histopathological levels. Another study demonstrated that NaF exposure led to dose-dependent skeletal malformations and developmental delay, further validating the zebrafish as a model for assessing dental and craniofacial toxicities.[26] Rosa et al. investigated the dentin–bone interface in zebrafish, offering valuable insights into mineralised tissue responses to chemical insult, including fluoride [16]

Dental implant materials are also under investigation. Zirconium oxide nanoparticles (ZrO_2NPs), commonly used in implant coatings, have been shown to cause acute toxicity, hatching delays, and craniofacial malformations at doses of$\geq$0.5 µg/mL in zebrafish embryos.[27] Additional studies using zebrafish have evaluated the toxicity of various metal alloys such as gold-palladium, silver-palladium, nickel-chromium, cobalt-chromium, and titanium. Among them, nickel-chromium exhibited the highest toxicity, with significant embryonic lethality and morphological abnormalities.[28] A study conducted by Zavareh in 2023 extended this toxicity analysis by modelling dental defects associated with fetal alcohol spectrum disorders (FASD), illustrating how zebrafish can integrate teratogen exposure with dental and craniofacial outcomes. Bioceramics, such as mineral trioxide aggregate (MTA) and Biodentine, have gained popularity in endodontics and restorative dentistry.[17] Their biocompatibility was evaluated using zebrafish embryos, which revealed that Biodentine showed superior compatibility over MTA, with fewer adverse developmental effects.[29] A study by Ohashi & de Souza Schacher supports these findings by highlighting the zebrafish's reliability for evaluating regenerative and endodontic materials.[14] Moreover, dental monomers such as Bisphenol A-glycidyl methacrylate (Bis-GMA) and methacrylate (MA) have been tested in zebrafish embryos. Bis-GMA at doses of 1 μM or higher resulted in craniofacial deformities and developmental abnormalities. Methacrylate exposure induced edema, cardiac malformations, and axial curvature defects during embryogenesis.[30] Vishnu et al. further discuss the implications of dental resin toxicity and the need for preclinical testing platforms like zebrafish in evaluating long-term safety.[31] In light of their sensitivity to chemical exposures, zebrafish offer a robust, cost-effective, and ethically favourable alternative for early-stage toxicity screening of dental materials.[31] They bridge the gap between in vitro assays and mammalian models, supporting safer innovations in clinical dentistry.

Table 1. Applications of zebrafish in dentomaxillofacial research

Research Area	Key Applications	Advantages of Zebrafish Model	Limitations
Tooth and Craniofacial Development	- Studying odontogenesis and tooth regeneration - Analysis of BMP, SHH, FGF pathways - Modeling craniofacial anomalies	- Lifelong tooth replacement (polyphyodonty) - Transparent embryos allow real-time imaging - High genetic similarity to humans	- Lack of cementum and permanent dentition - Differences in jaw and tooth positioning vs. mammals
Dental Materials Research	- Toxicity testing of fluoride, resin monomers, bioceramics, and nanoparticles - Evaluation of craniofacial toxicity	- Sensitive embryonic responses - High-throughput and cost-effective screening - OECD FET standardized testing	- Translational gaps due to physiological differences - Limited adult-stage material integration
Oral Cancer Studies	- OSCC xenograft modeling - Drug screening and therapeutic response - Tumor-stroma interaction studies	- 'Casper' mutants allow long-term imaging - Personalized drug response testing - Real-time tumor tracking	- Short lifespan limits long-term follow-up - Immune system differences compared to humans

Zebrafish in Oral Cancer Studies

Zebrafish (*Danio rerio*) have become an increasingly valuable model organism in oral cancer research due to their genetic manipulability, cost-effectiveness, and exceptional optical clarity during early development.[9] These characteristics allow for real-time, high-resolution visualisation of tumour formation, progression, angiogenesis, and metastasis, especially in embryos and larvae.[32] A significant advancement in adult zebrafish research is the development of the *Casper* mutant, which retains transparency throughout its lifespan via pigment gene knockout. This model enables long-term imaging and facilitates studies on xenotransplantation, gene editing, and drug testing.[33] Zebrafish have been successfully used to model multiple cancers, including melanoma, breast cancer, leukemia, and lung cancer.

Oral squamous cell carcinoma (OSCC) has also been a growing area of investigation using zebrafish. For instance, Wahbi et al. (2023) developed personalised zebrafish xenograft assays using OSCC patient samples, showing a strong correlation between in vivo tumour response and clinical drug efficacy, thereby demonstrating its utility in personalised cancer therapy design.[34] A novel cobalt–sulindac metal complex (Co-SLD) was tested on zebrafish embryos and CAL27 OSCC cells, where Co-SLD significantly inhibited cancer cell proliferation and migration at 10 μM without damaging surrounding normal tissues.[35] Similarly, zebrafish xenograft models were used to evaluate *Sandensolide*, a natural compound derived from *Sinularia flexibilis*, which showed potent antitumor activity against oral cancer cells.[36]

Recent studies have also explored the tumour microenvironment in zebrafish OSCC models. Wahbi et al. demonstrated that stromal cell interactions significantly modulate radiation response in head and neck squamous cell carcinoma (HNSCC), offering new insights into cancer-stroma dynamics using zebrafish xenografts.[37] Zebrafish xenograft assays have also proven useful for screening natural compounds with anti-cancer properties. Shen et al. emphasised zebrafish as a platform for evaluating both the therapeutic potential and toxicity of novel natural products in real-time.[38] The ability to integrate vascular imaging further enables tracking of drug effects on angiogenesis and metastasis in oral tumours.[39] Collectively, these findings —summarised in Table 1**,** support the zebrafish as a robust model for oral cancer research. Its applications span drug screening, xenotransplantation, tumour imaging, and personalised medicine—making it an indispensable tool in the advancement of oral oncology.

CONCLUSION

Zebrafish offer a valuable yet underutilised model in dentomaxillofacial research. Their rapid development, transparent embryos, genetic similarity to humans, and low maintenance costs make them suitable for studying craniofacial development, dental material toxicity, and oral cancer biology. They provide mechanistic insights into conserved pathways, serve as sensitive indicators of biocompatibility, and enable real-time imaging of tumour growth and drug response. Although anatomical differences and a lack of permanent dentition limit direct translation, zebrafish complement mammalian models by enabling ethical, rapid, and cost-effective studies, with future advances in genetics and imaging poised to expand their applications in dental science.

Zebrafish provide a promising complementary model in dental research, offering advantages in genetics, imaging, and regeneration. While anatomical differences limit direct translation, their use can reduce reliance on higher vertebrates. Future studies should expand applications in craniofacial biology, biomaterials, and oral oncology to strengthen translational relevance.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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