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Review article

Effectiveness of zebrafish models in understanding human diseases—A review of models

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ABSTRACT

Understanding the detailed mechanism behind every human disease, disorder, defect, and deficiency is a daunting task concerning the clinical diagnostic tools for patients. Hence, a closely resembling living or simulated model is of paramount interest for the development and testing of a probable novel drug for rectifying the conditions pertaining to the various ailments. The animal model that can be easily genetically manipulated to suit the study of the therapeutic motive is an indispensable asset and within the last few decades, the zebrafish models have proven their effectiveness by becoming such potent human disease models with their use being extended to various avenues of research to understand the underlying mechanisms of the diseases. As zebrafish are explored as model animals in understanding the molecular basis and genetics of many diseases owing to the 70% genetic homology between the human and zebrafish genes; new and fascinating facts about the diseases are being surfaced, establishing it as a very powerful tool for upcoming research. These prospective research areas can be explored in the near future using zebrafish as a model. In this review, the effectiveness of the zebrafish as an animal model against several human diseases such as osteoporosis, atrial fibrillation, Noonan syndrome, leukemia, autism spectrum disorders, etc. has been discussed.

1. Introduction

With the increasing complexities arising from the disease being caused by rapidly mutating pathogens or new infectious strains in modern times, the importance of understanding their pathogenicity is becoming the need of the hour. These studies leading to the understanding of the cellular and molecular mechanisms of such infections can only be undertaken in a suitable animal model. These animal models not only help researchers understand the progression of such diseases and their mechanisms, but also allow them to design various targeted therapies and drugs to help cure the disease [1]. One such popular animal model is that of the Zebrafish (*Danio rerio*), a teleost found in freshwater systems, which has been at the forefront of several research fields since the 1980s [2]. When zebrafish models started to be used in research, the primary focus was to contribute to the field of developmental biology, with thousands of zebrafish mutant models being identified with highly conserved disease genes among different species [3]. This finding made researchers aware of the importance of the zebrafish model in other research fields and subsequently led to gene cloning through rigorous expansion of gene mapping resources.

Today, zebrafish are being seen as a powerful model of acquired and genetic human diseases with increasing utility in translational research. The freshwater teleost is a popular animal model choice because of its high embryo yield, rapid reproduction rate,

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transparent embryos, economical maintenance, and fewer space requirements for setting up these zebrafish husbandries. Additionally, zebrafish embryos develop outside of the uterus, so they can be easily accessed post-fertilization for various studies. After the zebrafish genome sequencing project provided a comprehensive gene set in 2013, it was found that the genome possessed considerable homology with that of the human genome and that 70% of human genes had zebrafish orthologues [4]. The growth of its use in translational research can be extrapolated from Fig. 1A-B, which shows the increase of the use in zebrafish disease models over the years with the data being collected over the available literature from PubMed and Scopus databases (2000–2021).

In this review, we highlight the effectiveness of zebrafish as an animal model in understanding human diseases, genetic or otherwise, compiled around the various studies undertaken over the years bringing new knowledge of disease mechanisms previously unknown to the man with the help of different zebrafish models – mutant, knockdown, transgenic or otherwise. We are aware that some detailed articles specific to certain disease and disorder areas in relation to the modeling of zebrafish as a disease model already exist, but our goal here is to present a broad overview of the pathogenies associated to the modeling of the diseases in zebrafish models over the past two decades. Instead of providing a general overview of the entire field related to disease modeling in zebrafish, we have chosen to focus on a subsection of diseases in the fields of bone health, cardiovascular research, renal diseases, cancer, and blood ailments aimed at providing a glance understanding of the molecular mechanisms that lead to the diseases and specific zebrafish models that can be modeled around these molecular mechanisms to explore the disease condition. This article also discusses future areas of study that can be undertaken by using zebrafish as a model organism while also stating a number of exhaustive uses of the model organism in other fields of study not discussed at lengths in the paper.

2. Zebrafish–the making of an interesting translational model

One of the most interesting aspects of a zebrafish model is the rapid breeding amongst the models to generate stable disease model lines within 3–4 months. It is highly fertile, allowing it to produce at least 200 eggs per clutch every 2–3 days (Fig. 2A), which can be used for experiments as soon as 3 days post fertilization (dpf) [5,6]. The lucrative part about working with zebrafish larvae is the fact that the eggs are optically transparent in addition to having a diameter of about 0.7 mm making genetic manipulations through all the developmental stages feasible for the researchers [7]. This optical clarity observed during the initial stages of embryogenesis permits the researchers to image the detailed developmental processes concerning drug discovery, tissue regeneration, or pathogenesis of an infection, notably due to the homology of the zebrafish genome with that of humans (shown in Fig. 2B). The project undertaken to sequence zebrafish genome further calls to our attention that about 82% of the known human disease genes have zebrafish orthologs making it a highly interesting prospect for designing disease models within the last decade [4] driven by the modern technological advances (Fig. 2). This also allows us to presume that a considerably similar portion of the loci associated with genome-wide association studies (GWAS) having certain disease-causing genes can be tested using mutant disease models in zebrafish, suggesting a comparability of 368 BMD loci in mutant zebrafish to 393 BMD loci testable in a bigger model organism such as mutant mice as an example [8]. Few studies have been conducted in the past that have shown the potential of zebrafish to easily verify GWAS data [9,10]. Precision genome editing with the help of clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 and transcription

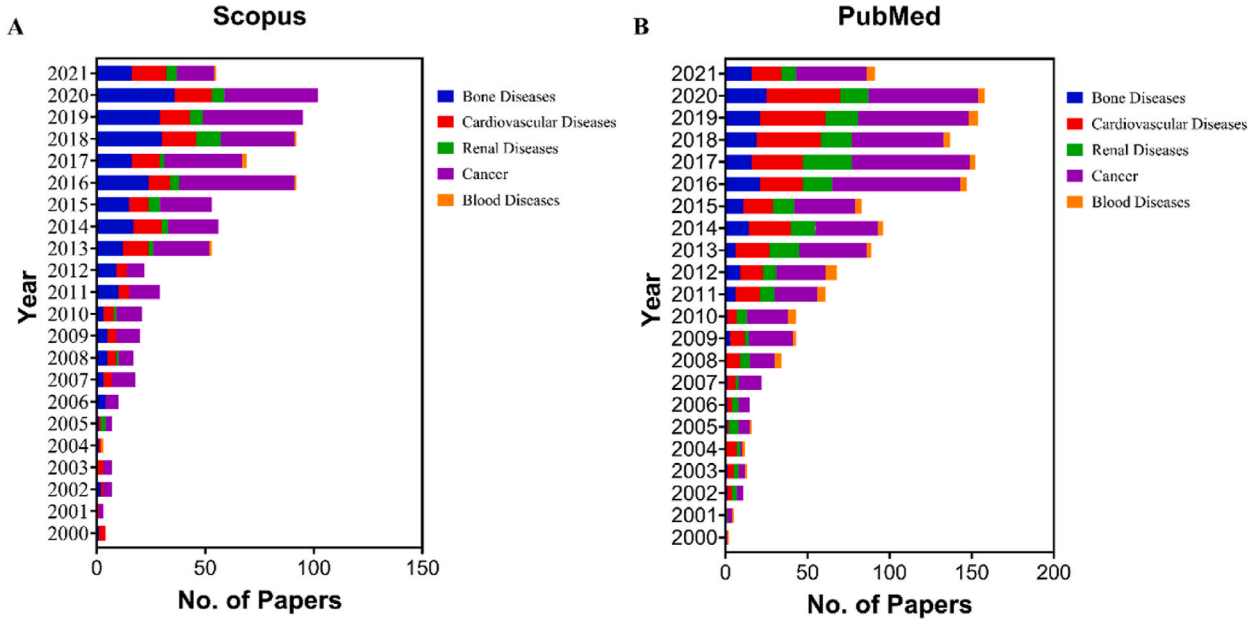

Fig. 1. The figure represents the progressive use of zebrafish disease models over the years from data that has been curated from **[A]** Scopus and **[B]** PubMed databases showing few of the broadly categorized fields where the zebrafish models are of great value.

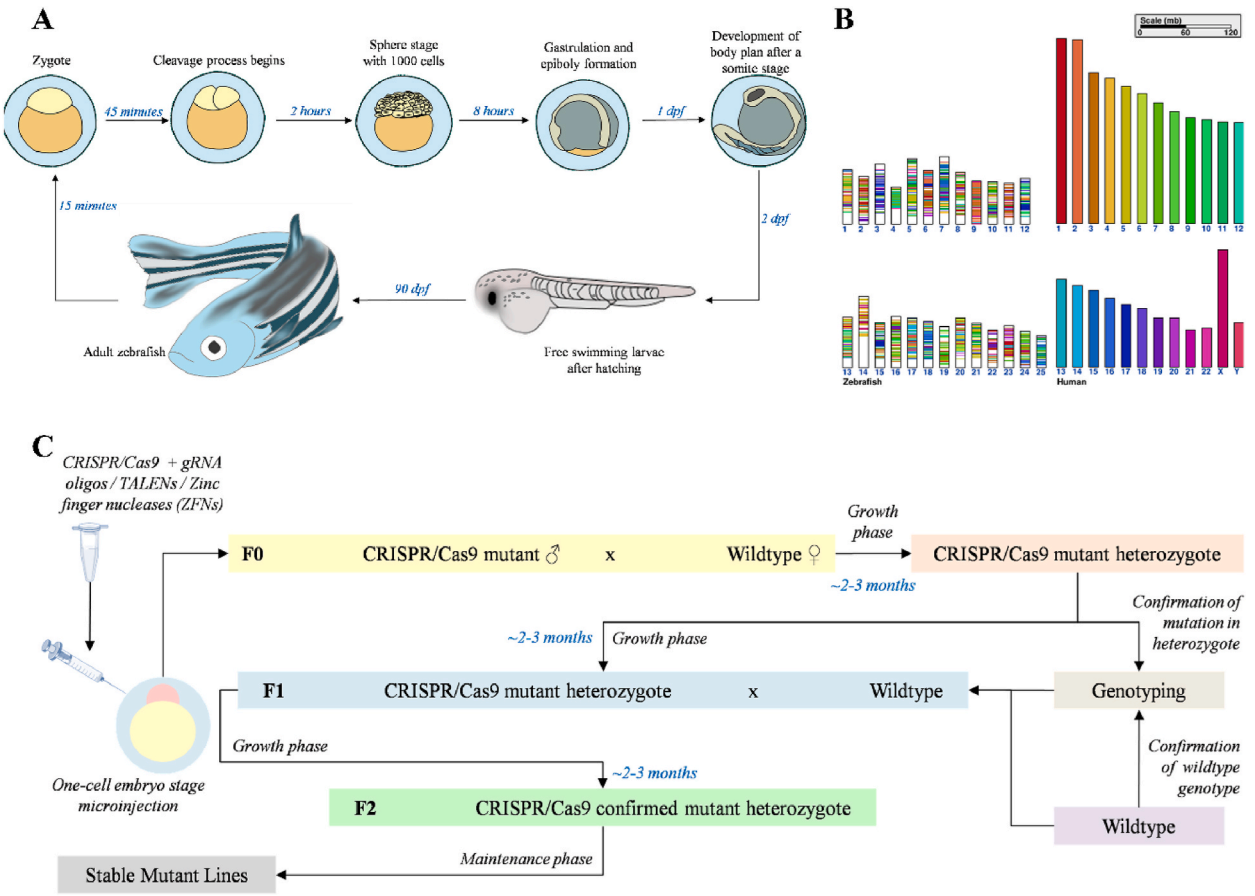

Fig. 2. This figure shows the schematic representations of **[A]** The life cycle of zebrafish which make it one of the most lucrative propositions as a model organism for diseases, **[B]** the comparison of the human and zebrafish genome with the help of Cinteny web server (http://cinteny.cchmc.org/) where the chromosomes are segregated and arranged with a particular color code which encodes for various syntenic regions between the two and **[C]** the mechanisms through which stable zebrafish mutant lines are created in the laboratory.

Table 1
Advantages of using zebrafish over rodents for developing disease models [14–16].

Basis	Zebrafish Models	Rodent Models
Size	Very small	Relatively bigger
Animal Care Costs	Quiet low	Quite high
Housing Requirements	Less space needed	Takes up a lot of space
Development	External	Internal
Number of offspring	~100–300 per week	~5–12 per month
Life span	~3–5 years	~2–3 years
F0 reverse genetic screens	Easily available and highly affordable	Not readily available and difficult to afford
F3 reverse genetic screens	Moderately available	Rarely available
External visibility of skeletal development	Easily viewable due to transparency at developmental stages	Not possible due to development in the uterus
Possibility of in-vivo fluorescence imaging	Highly possible	Low possibility
Orthologues count per human gene	~1 or >1	1
Genome-wide screening	Possible	Not possible
Genetic manipulation	Can be done easily	Harder process
Phenotyping	Rapid	Cumbersome
Neuroregeneration	Possible	Not possible
Telomere size	Short like humans with the age-related progression of decline	Long
Drug administration	Easier	Relatively difficult
3R strategy	Developed	Yet to be developed
Xenograft engraftment	Rapid	Slow
Experimental cycle	Short	Long
Ethical constraints	Very low	Quite a lot

activator-like effector nucleases (TALENS) are a few of these recent technological marvels that grant for the swift and streamlined production of site-specific genetic mutants in zebrafish of the tissue-specific study being performed [11] during a research (process shown in Fig. 2C). In one of the more recent studies performed for the efficient modeling of human diseases in zebrafish, it was shown that very precise point mutations can be introduced with high efficiency over multiple genes simultaneously using a variant of CBE4max-SpRY, which recognizes a variety of different PAMs, thus expanding on the base editor techniques for human disease model creation [12]. The reverse genetics techniques such as 'Targeting Induced Local Lesions In Genomes' (TILLING) might be used in zebrafish with ease to identify the loss-of-function or gain-of-function of the alleles in any gene in theory, thereby making it a well-rounded model for studying human diseases [13].

Moreover, zebrafish further give rise to two variants of models, namely, the larval and the adult models. The maintenance of these models is both space and cost-effective and in addition to this, their extended life spans in comparison to mice make it further interesting to scientists for developing new and effective disease models. The extent of its utility over rodent models is listed in Table 1.

Zebrafish have another very important tool in their immensely diverse but medically relevant toolkit; their potential in personalized regenerative medicine. Regenerative medicine fuelled by stem cell therapies has stepped into a dimension of personalized medicine that caters to any individual's need for targeted therapies based on the available medical data on them, such as pharmacogenomics and other genetic parameters. Due to the high regenerative potential of the zebrafish and its accessibility for genetic manipulations, zebrafish are being considered the future of personalized regenerative treatments, especially because the drug discoveries and their associated regenerative values found using zebrafish take lesser time compared to other models and can be made available to a greater number of patients at a lower cost owning to the homology between zebrafish and humans [17]. All these reasons and the fact that zebrafish make for a potent small system for screening multiple drugs during drug discovery make it one of the most powerful proponents of the 'tank-to-bedside' line of thought for in vivo models, which is at the core of any translational research [18]. The drug delivery is comparatively easier with zebrafish as water-soluble drugs can be directly administered by dissolving them in the water to be absorbed by the fish through their gills and skin [19] making for a non-invasive technique which reduces the stress associated with injections often seen in the murine systems. However, this does not limit researchers from using drug administration techniques such as intraperitoneal injections [20] or oral drug delivery [21], which allows the understanding of the bioavailability of the drug and other parameters critical to drug discovery and translational research. The extrapolation of the drug doses established using zebrafish models into higher mammals such as mice and subsequently humans would lead to further validation of the translational models of zebrafish and provide us with an affirmative nod towards the translational prowess of the models themselves, etching a new revolution in disease modeling and treatment discoveries in the near future. In such instances to develop precision medicine and the need to replace long and cumbersome complex trials to pace the proper conduction of drug trials, zebrafish models have stood out as a viable disease modeling system [22].

3. Effective zebrafish disease models

3.1. Bone diseases

One of the most important and unique features of the zebrafish model is that the models allow real-time live imaging of various biological processes like skeletal development and repair. This allows researchers to follow the skeletal development processes in zebrafish models for specifically designed bone diseases with ease. The embryonal stages of the zebrafish are considered to be one of

Table 2
Zebrafish models and their effectiveness in the study of bone diseases.

Disease Studied	Zebrafish Models	Effectiveness of the Study	Reference
Osteogenesis imperfecta (OI)	*Chihuahua (chi)*	Understanding the role of collagen in bone development through stress study of the endoplasmic reticulum in fibroblasts and osteoblasts	[25,26]
	frilly fins (frf)	Studying the less common form of OI caused by *bmp1* mutation affecting the formation of mature collagen I	[28,29]
Osteoporosis	*atp6v1h mutant*	Finding a new bone formation pathway as well as identifying a possible therapy	[30]
Osteopetrosis	*panther (fms)*	Provides an osteopetrosis disease study model	[31]
Osteoarthritis	*prg4a*$^{-/-}$*; prg4b*$^{-/-}$ *double mutant*	Studying wear and tear of cartilages present in joints due to depletion of lubricating proteins of synovial joints	[32]
Fibrodysplasia Ossificans Progressiva (FOP)	*acvr1-alk2 mutant*	Studying the role of *acvr* in dorsoventral patterning and understanding its role in the disease	[33]
Scoliosis	*fused somites (fss)*	Understanding the role of the Delta-Notch pathway in the progression of the disease	[34]
	leviathan	Study of the possibility of genetic factors playing a role in the disease	[35]
	zmynd10, *ift88*, *kif3b*, *uts2ra mutant*	Establishing a correlation between scoliosis and Parkinson's disease	[36]
Ankylosing spondylitis (AS) Klippel-Feil syndrome (KFS)	*dolphin, stocksteif*	Understanding the possible role of *cyp26b1* in AS and KFS	[37]
Craniosynostosis	*stocksteif*	Understanding that osteoblast differentiation defects can induce the disease	[44]
	tcf12/twist1b double mutant	Using CRISPR technology for understanding the disease progression	[38]

the most powerful models for bone research with researchers reportedly using them for studying the process of osteogenesis since the first mineralized vertebrae can already be visualized after five days of the fertilization of the egg [23]. Table 2 lists the different zebrafish models developed for various bone-related diseases along with their effectiveness.

One such bone disease of great relevance is Osteogenesis imperfecta (OI) which is also called the brittle bone disease caused by mutations in the collagen genes *col1a1* or *col1a2* [24]. The first zebrafish mutant model characterized in the year 2003 for the bone disease was known as *chihuahua (chi)* [25], which mapped for the mutation to *collagen1a1 (col1a1)* and presented similar symptoms of OI (as depicted in Fig. 3B–C). It also led to a better understanding of the role of collagen in bone development through a stress study of the endoplasmic reticulum in fibroblasts and osteoblasts [26]. The study with the *chi* model of the zebrafish designed to mimic the classical dominant OI symptoms found that the deformities and fractures observed in the zebrafish model were a result of altered bone quality brought about by a heterozygous glycine substitution in α1 chain of the type I collagen. Zebrafish mutants for col1a2 and col1a1b were identified as presenting the disease phenotype during recent studies [27]. Zebrafish models with mutant *bmp1* are known as *frilly fins* (*frf*) [28] which facilitates the study of a less common form of Osteogenesis imperfecta which results due to mutation of the bone morphogenetic protein (*BMP1*), which is known to generate mature collagen I [29] causing alteration in the osteoblast morphology which appears cuboidal in shape. The assumptions that it was a result of reduced adhesion and not merely a defect in the osteoblast was verified later through their in-vitro studies where the osteoblast cultured on collagen-deficient bone matrix showcased somewhat rounded morphology instead of its flattened morphology when viewed on a purified mineralized collagen matrix. Through this study, it was understood that autosomal recessive OI with an increased bone matrix is generally the result of insufficient removal of the C-propeptide from collagen-I.

Osteoporosis is a bone disease characterized by porous bones due to the increased osteoclastic action or the inadequacy of osteoblasts in replacing resorbed bone. To study this disease, a mutant zebrafish *atp6v1h* model (represented in Fig. 3A) was created that showcased a new bone formation pathway along with identifying a possible therapy for such patients [30]. This study allowed for the understanding of the crucial role of activation of *mmp9/mmp13* with respect to osteoporosis and led to the proposal of a novel model of action related to therapeutic entry points for osteoporosis and related diseases. Although no orthologues are available in zebrafish for the known human osteopetrosis genes that cause dense but brittle bones, a zebrafish mutant model for the *c-fms* oncogene, *panther* has been identified to provide an osteopetrosis model [31]. The study outcome also suggested that the dysfunction of osteoclasts can lead to an abnormal vein formation through the gathering of mononuclear precursor cells in congested spaces of haemal arches and blood vessels suggesting a role of certain factors triggering osteoclastogenesis at these sites.

To study osteoarthritis which is caused by the wear and tear of cartilage present in the joints, a genetic zebrafish double mutant model for *prg4a* and *prg4b* was developed in which both knockout genes are known to encode essential lubricating proteins of synovial joints [32] and the severity of the disease aggravates with aging, just like in humans. The study found that the jaw and fin joints of the model require lubricin for their maintenance which is a molecular lubricant similar to synovial joints making it a prospective model for the study of synovial specializations including the process of cavitation and in-depth understanding of the development and progression of synovial joint diseases.

Models such as *acvr1* zebrafish mutants presented phenotypes associated with Fibrodysplasia Ossificans Progressiva (FOP) which is a rare autosomal disorder where connective tissues, as well as muscles, transform into bone [33], allowing researchers to use the model in better understanding the disease and mechanisms related to the pathophysiology of the disease. The development of this model allows for future investigation of injury models, building a better understanding of the progression of the disease. There are models designed to study spine curvature diseases such as scoliosis which are presented primarily due to gene mutations in the Delta-Notch pathway. The zebrafish mutant model *fused somites* (fss), which contains a mutant of the *tbx6* gene of the Delta-Notch pathway [34], and the zebrafish model called *leviathan* (shown in Fig. 3) has a mutation of the *col8a1a* gene but completely unrelated to the Delta-Notch pathway [35] are used to study scoliosis as of late. *Leviathan* was used to probe into the possibility of genetic factors playing a role in scoliosis while at the same time proposing a novel mechanism for the formation of vertebral columns arising from the aberrant deposition of bone in misshapen notochord tissue regions independent of somitogenesis defects. The former study with the

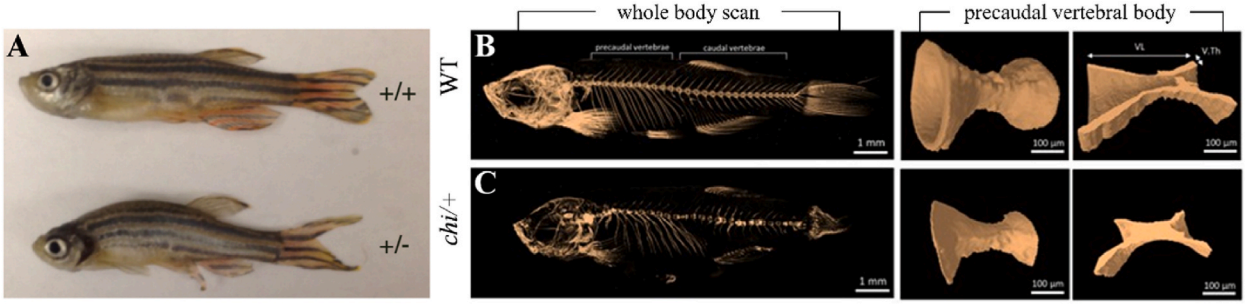

Fig. 3. The figure shows two models of zebrafish, used effectively to treat bone diseases. **[A]** The zebrafish having the *atp6V1h* mutation (±) shows a curved phenotype when compared to its wild-type counterpart (+/+) due to the curvature of the spine. **[B]** Shows the scan of wild-type zebrafish alongside the longitudinal cut of the vertebral body while **[C]** represents the scan of the *chi*/+ mutant showing deformities of the fins and ribs along with heterogeneous skull mineralization while also demonstrating an odd geometry and mineralization of hard tissues. Adapted with permission from references [26,30].

model helped identify the relationship of certain gene mutations involved in the patterning of somites through signaling pathways arising from the notochord. Quite recently, using zebrafish mutant models for *zmynd10*, *ift88*, *kif3b,* and *uts2ra,* a correlation was established between Parkinson's and scoliosis [36]. The research showed that the severity of the spine curvature has a correlation with the severity of the zebrafish phenotype and that urotensin provides adrenergic signals through the cerebrospinal fluid (CSF) activating the slow-twitch muscles portraying a role in the straightening of the axis, allowing us to speculate on the aforementioned correlation.

A *cyp26b1* mutant zebrafish model called *dolphin* and *stocksteif* has been successfully shown to be useful for studies of bone diseases such as Ankylosing spondylitis (AS) and Klippel-Feil syndrome (KFS) [37] with *stocksteif* being used as a model of craniosynostosis [38, 39] as well. The studies helped to understand that the skeletogenesis of zebrafish is closely regulated by adequate levels of *retinoic acid* (RA) and critically controlled c*yp26b1* activity and that *cyp26b1*-dependent *RA* restriction is required to properly control osteoblast biology and bone formation. A *tcf12/twist1b* double mutant model has also been designed to study craniosynostosis disease using CRISPR technology [38]. The study helped to easily detect cells expressing *tcf12* in cranial sutures, skull bone, and neural tissues in the zebrafish model, signifying that these heterozygous mutations can affect maintaining the patency of sutures. Zebrafish can also be used to provide insight into transgenesis. This is because transgenic reporter models have found great use as of late to visualize the skeletal system growth and regeneration as well as the cellular behaviors based on genetic context to gain an understanding of the molecular mechanisms related to the disease etiology [40].

In addition to these, there have been several transgenic models of zebrafish which have been used to study the various genetic pathways in association with the cell types involved in the disease pathogenesis of their targets. Osteoblasts have been studied using *Tg (Ola.sp7:mCherry)*^{zf131} and *Tg (Ola.sp7:NLS-GFP)*^{zf132} with *osterix (osx)* as a genetic marker [39] while *Tg(-2.2col10a1a:GFP)*^{ck3} that has been known to express GFP in the presence of *col10a1* promoter which unlike mammals is not limited to chondrocytes in zebrafish and thereby makes for an excellent model for studying molecular mechanisms indicative of both chondrogenesis as well as osteogenesis [41]. The osteoclast studies in relation to multiple diseases and skeletal regeneration have been investigated using transgenic zebrafish models such as *Tg(ctsk:DsRed)* [42] and *Tg(trap:GFP-CAAX)*^{ou2031} [43] that use *ctsk* and *trap* as markers for osteoclastogenesis.

3.2. Cardiovascular diseases

The embryonic zebrafish heart can be easily inspected in live zebrafish due to its position on the ventral side, thus allowing researchers to understand the mechanisms involved in the development and functioning of the heart. This is not the only attractive feature of the zebrafish model, as its effectiveness as a disease model is increased by the fact that they are not dependent on circulation initially during its early developmental phase, but rather remains oxygenated by passive diffusion. This provides the researchers an opportunity to probe into the disease progressions of the various cardiac phenotypes. Table 3 describes the various zebrafish models that have been used effectively to study many of the different types of cardiovascular disease.

Out of the many effective phenotypes of heart-specific mutant lines obtained for studying various cardiovascular diseases, one of the most useful lines is the *silent heart* (*sih*) model [45] which is perfect for the study of various molecular pathways involved in cardiac disorders as well as the structural changes occurring due to these disease conditions. The study with the *sih* model provided the first animal model for *tnnt2* deficiency that is responsible for the proper assembly of the cardiac sarcomere making the heart muscle non-functional. Identification of the molecule SB216763 allowed researchers to understand the role of the Wnt signaling pathway in the pathophysiology of arrhythmogenic cardiomyopathy studied in the zebrafish model obtained with a mutated plakoglobin [46]. The study with the plakoglobin mutated model (as shown in Fig. 4A) helped to elucidate that aberrant trafficking of proteins related to the functioning of intercalated discs is the main cause of myocyte injury in arrhythmogenic cardiomyopathy (ACM) along with various electrical abnormalities.

The potassium interacting channel 1 gene (*kcip1*) which is associated with atrial fibrillation (AF) was shown to play a role in the modulation of atrial rate in the heart of zebrafish, indicating a possible target for AF treatment [10]. The results obtained using zebrafish mutated *kcip1* showed that the mRNA level of the *kcip1* gene and its protein determined by the intronic CNV present in the *kcip1* gene can be linked to high atrial rates and could be a possible future target for the disease treatment. Long QT syndrome type 2 (LQT2) zebrafish models with a mutated potassium voltage-gated channel subfamily H member 2 (*kcnh2*) have been used to understand severe cardiac repolarization and long ventricular depolarization associated [47] with the loss of *kcnh2* activity [48]. The results

Table 3
Zebrafish models and their effectiveness in the study of cardiovascular diseases and renal diseases.

Renal Diseases			
Glomerular diseases	*Tg(podocin: GFP)*	Studies related to podocytes and their role in the progression of glomerular diseases	[64]
Noonan syndrome	*sos2-acp1mutant*	Studying the role of *sos2* and *acp1* in renal tubule alterations and insufficient glomerular functions	[65]
Nephrotic syndrome disease	*plce1 knockdown*	Studying the role of *plce1* in causing oedemas and effacement of podocytes along with the progression of the disease conditions	[66]
Steroid-resistant nephrotic syndrome	*Tg(wt1b:EGFP)*	Understanding the role of FAT1 in the onset of the disease conditions	[67]
Diabetic neuropathy	*elmo1 mutant*	Establishing the role of the *elmo1* gene in the diabetic conditions	[68]
Fanconi syndrome	*ctns mutant*	Undertaking various other nephropathic cystinosis studies	[69]
Autosomal dominant polycystic kidney disorder (ADPKD)	*double bubble, fleer*	Studying the disease pathophysiology and understanding the role of Na^+/K^+ ATPase mislocation in the disease progression	[70]

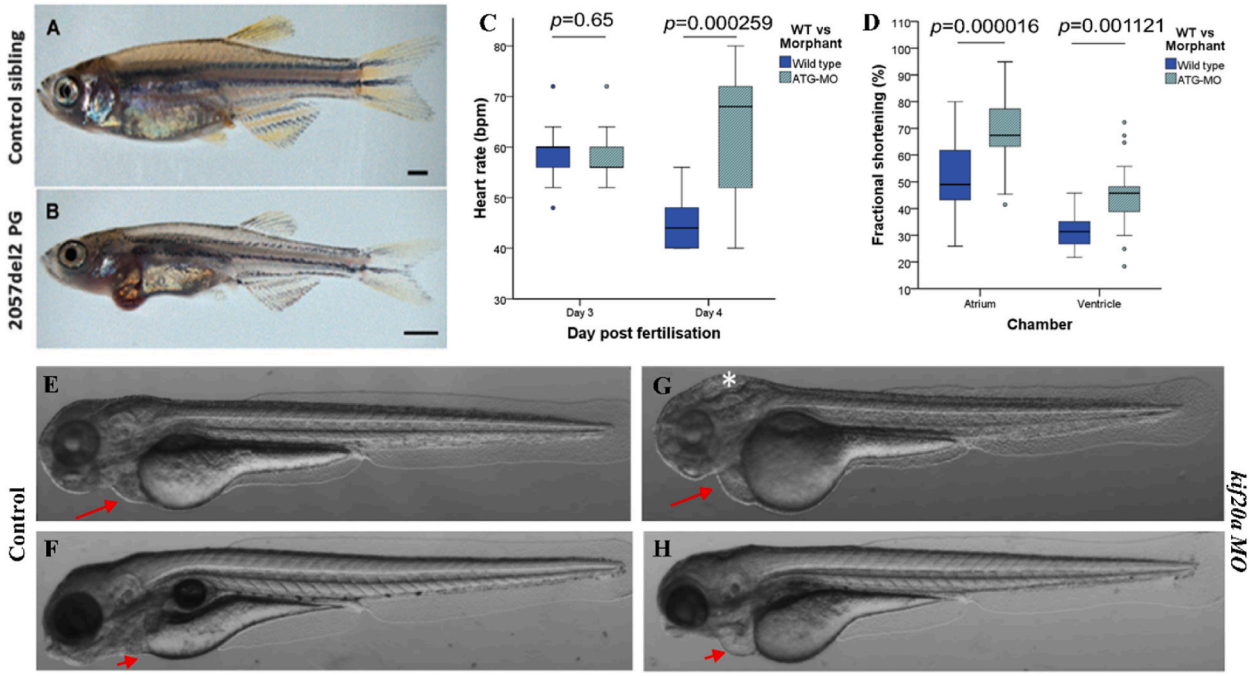

Fig. 4. The figure shows zebrafish models used in treating cardiac-related issues. **[A-B]** Shows the morphology of the **[A]** 5-week-old control zebrafish and the **[B]** zebrafish with a mutated plakoglobin demonstrating arrhythmogenic cardiomyopathy (scaled to 1 mm); **[C-D]** Represents the cardiac function analysis performed in the control and *kif20a* morphants where **[C]** the heart rate is compared between the control and the *kif20a* morphants at 3 days post fertilization (dpf) and 4 dpf resulting in an appreciable rise in the heart rate at 4 dpf associated with progressive cardiac failure **[D]** A significant fractional shortening can be observed at 4dpf in both atrium and ventricle in morphants of the morphants when compared to the control but based on more outliers and systolic failure could be predicted; **[E-H]** Represents the control and *kif20a* mutant models where it can be observed that **[G-H]** pronounced cardiac edema (denoted by the red arrows) can be observed in morphants at both 3 and 4 dpf while cerebral edema in morphants (denoted by *) could only be seen at 3 dpf which was not present in the **[E-F]** controls at 3 and 4 dpf. Adapted with permission from references [46,52]

obtained using Long QT syndrome type 2 zebrafish models demonstrated the functional abnormalities of E637K mutations in terms of cardiac polarizations. Mutations in *prrx1a* and *prrx1b* in the zebrafish model for human *prrx1*, a transcription factor associated with AF, showed that the duration of the atrial potential is modulated by the slightest of changes in *prrx1* expression [49]. The study helped identify a *prrx1* upstream enhancer for its promoter and was found to be modulated by single-nucleotide polymorphism (SNP) that has an inverse action on *prrx1* expression. The conclusions drawn from the use of the zebrafish model implicated *prrx1* as the causative gene of AF.

Dilated cardiomyopathies can be studied with the help of the zebrafish heat shock protein, beta 7 (*hspb7*) mutant model [50] and integrin-linked kinase (*ilk*) mutant model, *main squeeze* (*msq*) [51]. The study undertaken with the *hspb7* zebrafish model provided the basic understanding of how the *hspb7* gene regulated the proteostatic mechanisms functioning in the cardiomyocytes giving rise to a new stress-dependent model for cardiomyopathy in humans while the zebrafish model *msq* contributed to the scientific knowledge about cardiomyopathy by finding a relationship between the laminin-integrin-*ilk* mutations with the disease condition and heart failure. The models of mutant *kif20a* of zebrafish, as demonstrated in Fig. 4C–H, are associated with studies of congenital cardiomyopathy and the studies suggest that *kif20a* is conserved in developing the heart through evolution [52]. Through the study with the zebrafish model, it was shown that translational blocking of the *kif20a* gene promoted a cardiomyopathy-like phenotype, which showed the functionality of the gene for proper heart function. Zebrafish models obtained by genome editing using the CRISPR-Cas9 technique of the gene *pbx4* are associated with congenital heart defect studies [53] where it acts as a 'genetic modifier' that promotes the disease condition caused by loss of function of the gene *hand2*. Valvulopathies are a form of cardiovascular disease that can cause fatal heart failure in patients. Studies in zebrafish *lmcd1* and *tensin1* mutant models have strengthened our understanding of mitral valve prolapse (MVP), which is one of the most common valvulopathy observed [9]. The study with these two zebrafish models provided proof that both the genes which have been previously implicated in the proliferation and migration of cells, contribute to the degeneration of the mitral valve during valve development. The genes *lcmd1* and *tensin1* are now considered important genes in the pathogenesis of MVP.

The zebrafish *gridlock* (*grl*) mutant models are very effective in studying aortic coarctations [54,55] and their causative mechanisms [56]. The studies with the *grl* model of zebrafish showed that the gene *hlh* is necessary for the proper functioning of the aorta which otherwise would form a phenotype resembling coarctation of the aorta. The zebrafish *slow mo* mutant is a model for bradycardia [57] whereas models such as *tremblor*, *santa,* and *reggae* are used to study diseases related to the rhythmicity of the heart [58]. The *slow mo*

(smo) model helped to understand the role of a form of current associated with the nervous system, I_h, and its contribution towards the pacemaking ability of the heart. The potential of cardiovascular disease modeling in zebrafish also makes it a lucrative model to lead into studies dealing with precision medicine for diseases, thus letting us study the pharmacological responses associated with novel drugs awaiting translational mobility [59].

3.3. Renal diseases

The zebrafish has pronephros which comprises two nephrons characterized by fused glomerulus along with paired bilateral ducts [60] which have established zebrafish models for studying renal diseases that affects the development of nephrons and their physiology [61]. The podocyte epithelial cells of the glomerulus are a potent target of many causative agents of renal diseases and hence a lot of the more recent research employing renal disease zebrafish models include podocytopathies [62]. The various models of zebrafish developed to investigate renal diseases can be found in Table 3.

The transgenic models of zebrafish give an outstanding prospect for the development and regeneration of podocytes in modeled zebrafish [63]. The zebrafish transgenic line model *Tg*(*podocin:GFP*) has shown that the morphology between mammalian and zebrafish podocytes is conserved [64] which has led to the use of zebrafish models to understand the progression of various glomerular diseases. According to the study, the model is potentially equipped to facilitate real-time imaging, sorting through FACS and molecular

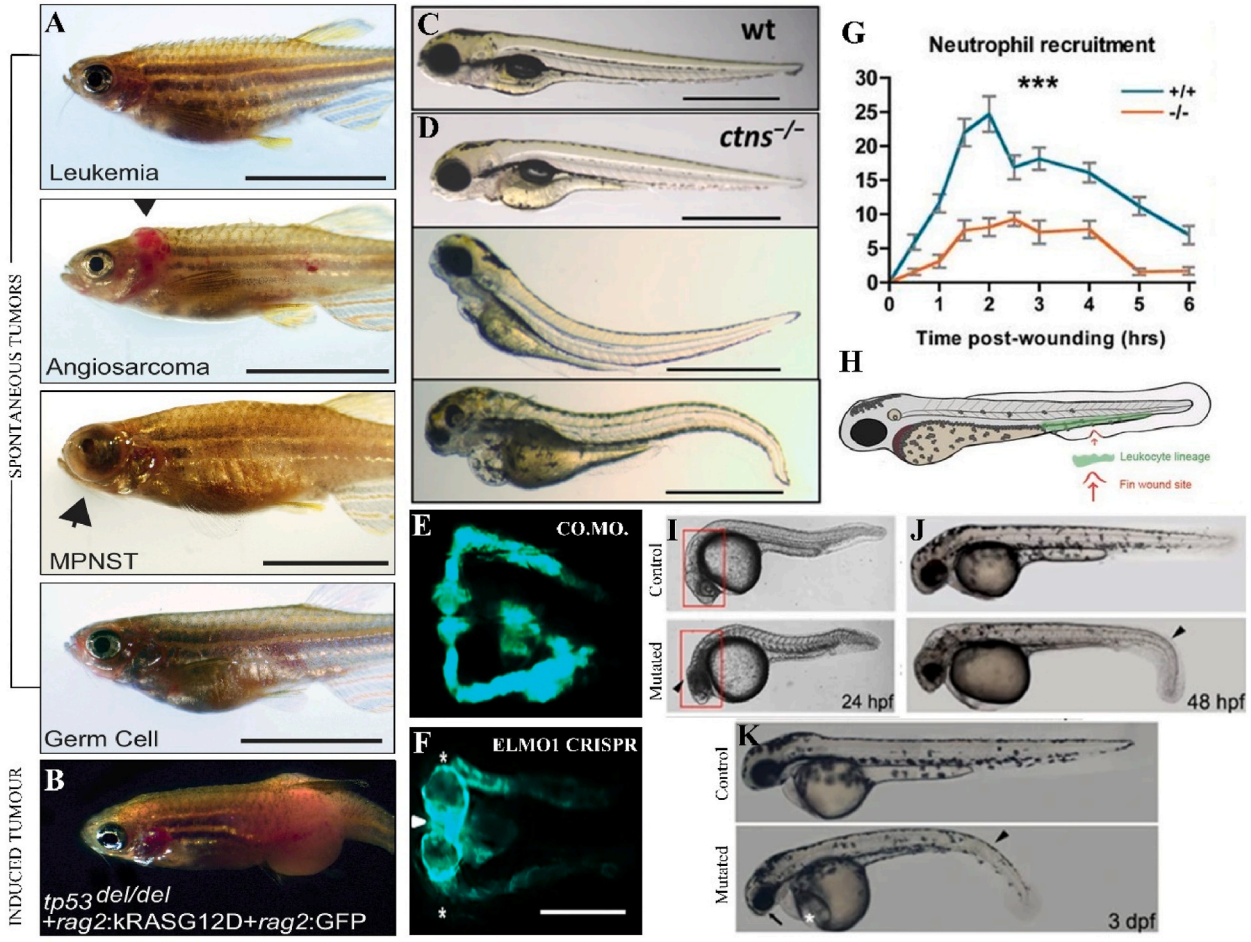

Fig. 5. This figure demonstrates the zebrafish models utilized in understanding human diseases. **[A-B]** Shows the zebrafish model, *CG1 tp53*$^{del/del}$ used for studying spontaneous and induced tumors; **[C-D]** Even though the wild-type zebrafish larva shows a normal morphology, the *ctns*−/− mutant shows deformities such as growth retardation **[D, upper]** denoted by the bigger yolk, **[D, middle and lower]** bent head, and bulging eyes with mild and severe deformities; **[E-F]** In comparison to the **[E]** control morphant (Co.Mo.), **[F]** *ELMO1* crispant (*ELMO1* CRISPR) showed an enlarged glomerulus (depicted by the white arrowhead) and shortened pronephric neck (denoted by white asterisk) suggesting an adverse effect of hyperglycemia upon the pronephric structure of zebrafishes; **[G]** The effectiveness of the *WASp1*$^{-/-}$ model in the timed recruitment of neutrophils when compared to wild-type zebrafish larvae and **[H]** the schematic diagram of the *WASp1*$^{-/-}$ model; **[I–K]** Shows the various models and experimental results obtained for studies related to blood disease models. The different phenotypes of *rps19* homozygous mutants at different timed stages – **[I]** 24hpf, **[J]** 48hpf, and **[K]** 3dpf are shown. Adapted with permission from references [68,69,77,89,95].

profiling of zebrafish podocytes, as well as HTS of functional genes by injecting morpholino. Noonan syndrome observed in humans and kidney abnormalities can be studied in the zebrafish mutant models for SOS Ras/Rho guanine nucleotide exchange factor 2 (*sos2*) and acid phosphatase 1 (*acp1*), which results in morphological alterations in the renal tubule and low dextran clearance suggesting insufficient glomerular function and damaged tubular flow [65]. The study led to the discovery of eight loci associated with kidney functionality, as well as to establish the roles of *sos2* and *acp1* in relation to kidney development in embryos. Furthermore, the zebrafish model gave rise to functional systemic models for studying gene perturbations with respect to the embryonic renal system. The knockdown of the phospholipase C epsilon (*plce1*) gene in zebrafish embryos has been implicated in causing edema in phenotypes along with podocyte effacement observed in the disease condition of nephrotic syndrome [66]. Through the study, a conclusion was drawn stating that the *plce1* based arrest of the development of glomerulus was reversible through glucocorticoid or cyclosporine A treatment although the mechanism of its action couldn't be figured out. An interaction was also established between IQ motif–containing GTPase-activating protein 1 (*IQGAP1*) and *plce1* through this multifaceted study, which further indicated that *plce1* could serve the purpose of an 'assembly scaffold' necessary for the development of the glomerulus through its role in organizing a complex of molecules necessary for the proper glomerular morphogenetic processes.

Tg(*wt1b:EGFP*) zebrafish model with a knocked down FAT atypical cadherin 1 (*fat1*) has been developed for studies of steroid-resistant nephrotic syndrome [67]. Researchers through the study model of the transgenic zebrafish line demonstrated that in case of a low expression of *fat1*, there is impairment in the activity of *rac1* and *cdc42* suggesting that the activation of the two GTPases would partially restore functionality to the defective cell migration caused by *fat1* knockdown. This mechanistic theory tested out to be true when *rac1/cdc42* activators were introduced in the study mitigating the disease phenotype.

The zebrafish *elmo1* mutant model (as can be observed in Fig. 5E and F) is a model of diabetic neuropathy that has established the role of the *elmo1* gene under diabetic conditions [68]. The study findings clearly define the protective role of *elmo1* through the anti-apoptotic route in hyperglycaemic conditions, thus predicting that favorable up-regulation of the *elmo1* gene would be beneficial in the study of diabetic nephropathy. Nephropathic cystinosis zebrafish models (Fig. 5C and D) with a mutant cystinonin (*ctns*) gene have been used to study renal Fanconi syndrome [69]. The model was validated through their in vivo studies recording the various phenotypic similarities of the model to the human disease condition, providing the basis for future therapeutic screening for drugs. The disease condition autosomal dominant polycystic kidney disorder (ADPKD) is often associated with the Na^+/K^+ ATPase mislocation, which was studied using the *double bubble* [60] model of zebrafish. This study also shows the role of the model in assessing cell polarity. This study allowed the zebrafish model for various other studies related to the disease. *Elipsa* and *fleer* can be used as zebrafish disease mutant models in the study of another disease condition called Senior-Loken syndrome [60].

3.4. Cancer

Over the years, cancer has been a looming topic in the minds of researchers across the globe, with one of the biggest challenges associated with cancer studies being intratumor heterogeneity. Cancer is considered to be a collection of genetically variable diseases with certain commonalities at the molecular level, and hence it is important to understand the molecular mechanisms at play to address any progressing malignancy. Such studies require models, and few of the most important models for cancer studies are created in zebrafish due to the relative ease in gene manipulations that can be done in it for the studying of a variety of cancers as well as the initial transparency exhibited by the zebrafish embryos and larvae. This transparency quotient led to the development of a zebrafish model *casper*, that remains transparent throughout adulthood allowing the visualization of cancer formation and its gradual progression [71].

The zebrafish-mutated model $tp53^{M214K}$ is one of the first mutation models found by genetic screening techniques and it helped to study multiple cancer types such as peripheral nerve sheath tumor (PNST), breast cancer, brain tumor and leukemia [72]. A similar PNST study can also be carried out in the zebrafish model $brca2^{Q658X}$-$tp53^{M214K}$ [73] while a cancer model was created using the zebrafish-mutated model $BRAF^{V600E}$-$tp53^{-/-}$ [74] that lost its malignancy in the absence of $tp53^{-/-}$ mutations [75]. The findings from zebrafish model $brca2^{Q658X}$-$tp53^{M214K}$ studies showed that *brca2* genotype and sex of the model act as independent variables affecting the outcome of survival in fishes bearing the form of cancer while the studies with $BRAF^{V600E}$-$tp53^{-/-}$ models showed for the first time a 'cooperative genetic interaction' which resulted in the cancer of zebrafish posing the models potential for understanding the progression of the development of cancer genetically adding to the pathological relevance of the *BRAF* mutation.

Zebrafish mutated models $rag2{:}KRAS^{G12D}$ and *CG1*-$tp53^{-/-}$ (Fig. 5A-B) are implicated in the study of rhabdomyosarcoma (RMS) [76] and a combination of sarcoma and leukemia studies [77] respectively. The study undertaken with the $rag2{:}KRAS^{G12D}$ mutated model of zebrafish suggested that the molecular pathways involved in embryonal rhabdomyosarcoma (ERMS) are conserved in both zebrafish and humans in addition to being potential isolation models for cancer stem cells for the disease thus allowing for a better understanding of the molecular and regulatory pathways associated in the onset of the disease. On the other hand, the work done with the zebrafish mutated model *CG1*-$tp53^{-/-}$ showed that ERMS metastasis is greatly affected by the loss of *tp53* that accounts for the aggressive invasiveness of RMS in the disruption of the *tp53* pathway. A model designed to study Costello syndrome called $HRAS^{G12V}$ (represented in Fig. 5) can also be used to study a variety of lymphomas, melanomas, and sarcomas [78]. The results of the study show that *HRAS* activation induced by the absence of *tp53* causes overgrowths in the CNS that are often associated with simultaneous inactivation of *p53* leading to age-related aggravation of the disease phenotype. A zebrafish model *ptfa1:KRASG12V* has been developed to study pancreatic adenocarcinoma [79] showed upregulation of hedgehog pathway components, indicating that the disease phenotype is affected by the hedgehog pathway. Another model $tg{:}BRAF^{V600E}$ has been implicated in the study of thyroid carcinomas [80] whose study results showed for the first time the role of *TWIST* gene expression downstream of $BRAF^{V600E}$ gene mutations.

Models like *rag2:mMyc* are used for the study of T-cell acute lymphoid leukemia (T-ALL) [81], *spi1:tel-jak2a* for studies of T-ALL and chronic myeloid leukemia (CML) [82,83] and *spi1:MYST3/NOCA2* for studies of acute lymphoid myeloma (AML) [84]. The use of the *spi1:tel-jak2a* model for T-ALL and CML provided insight into the etiology of the disease condition arising from alternative fusions of *TEL-JAK2* exerting its oncogenic effect in a cell lineage-specific manner caused by probable downstream signaling differences. The outcome of the *spi1:MYST3/NOCA2* zebrafish model study confirmed the transforming properties of *MYST3/NOCA2* previously observed in murine species and hematopoietic stem cells. A list of the effective zebrafish models implicated in the translation of cancer research can be found in Table 4.

3.5. Blood diseases

Zebrafish form great animal models for studying diseases related to blood and blood cells since mutants obtained through various screening and transgenic processes present an almost accurate model of human hematopoietic disease. The blood system and the pathways related to the synthesis of blood are very similar and more or less conserved in both mammals and zebrafish which also boosts the translational potential of these models greatly [85]. During the forward genetic screening, the first animal model for congenital sideroblastic anemia disease was discovered and the zebrafish mutant model for *δ-aminolevulinate synthase* (*ALAS-2*) was called *sauternes* [86]. The study showed that the *sauternes* model of zebrafish is heme deficient probably caused by a defect in the heme biosynthesis pathway and suggested a role of the *alas2* gene in the differentiation of adult blood cells. The severity of the heme-deficient phenotype of the zebrafish model was shown to depend on the expression of the *globin* gene. The zebrafish *yquem* model with mutations in the *uroporphyrinogen decarboxylase* (UROD) gene [87] and the *dracula* model with mutations in the *ferrochelatase* gene [88] are considered good models to study human porphyrias, both of which relate to faulty heme biosynthesis pathways. The study with the *yquem* model of zebrafish provides insight into the first attempt at in vivo gene therapy for the disease condition of porphyria. The study also suggested there was a need for a *urod* promoter or enhancer in the study to completely alleviate the disease phenotype. The research involving the *dracula* model of zebrafish proposed the presence of maternal deposition of heme, *ferrochelatase* activity, or *fch* gene in the yolk of the embryo accounting for the survival of the *fch* gene mutants studied with the help of the zebrafish model of porphyria.

For studies related to Diamond-Blackfan anemia (DBA), zebrafish genetic models were developed for deficiencies of the ribosomal protein S19 (*rps19*) (as shown in Fig. 5I–K) and the ribosomal protein L11 (rpl11), leading to a significant contribution to the study undertaken [89]. The outcome of the study interestingly showed that translational defects of the *globin* gene were partially rescued by treatment with L-leucine which is known to work in correlation with the mTOR pathway in the *rps19* and *rpl11* mutant models, suggesting a role for L-leucine in activating the translational processes of erythroid cells allowing for a better understanding of the

Table 4
Zebrafish models and their effectiveness in the study of cancer and blood diseases.

Disease Studied	Zebrafish Models	Effectiveness of the Study	Reference
Cancer			
Peripheral nerve sheath tumor (PNST)	*tp53^{M214K} mutant*	Studying the molecular mechanisms leading to cancer formation and its progression	[72]
	brca2^{Q658X}-tp53^{M214K} mutant	Undertaking the studies related to PNST	[73]
Melanoma	*BRAF^{V600E}-tp53$^{-/-}$ mutant*	Malignancy studies in the absence or presence of *tp53*	[74,75]
Rhabdomyosarcoma (RMS)	*rag2:KRAS^{G12D} mutant*	Undertaking tumorogenesis studies to understand the progression of the disease better	[76]
Pancreatic adenocarcinoma	*ptfa1:KRAS^{G12V} mutant*	Undertaking studies related to the human pancreatic adenocarcinoma	[79]
Thyroid carcinoma	*tg:BRAF^{V600E} mutant*	Studying a novel potential target responsible for *BRAF^{V600E}*-driven thyroid follicle transformation	[80]
Leukemia	*rag2:mMyc mutant*	Undertaking studies related to T-ALL	[81]
	spi1:tel-jak2a mutant	Undertaking studies related to T-ALL and CML	[82,83]
	spi1:MYST3/NOCA2 mutant	Undertaking studies related to AML	[84]
Blood Diseases			
Sideroblastic anemia	*sauternes*	Studying the role of *alas2* in the progression of sideroblastic anemia	[86]
Porphyrias	*yquem*	Understanding the role of the *urod* gene in the heme biosynthesis pathway and the progression of the disease	[87]
	dracula	Studying the effect of *ferrochelatase* gene mutations in the heme biosynthesis pathway and the progression of the disease	[88]
Diamond-Blackfan anemia (DBA)	*rps19-rpl11 mutant*	Understanding the correlation between protein reduction and defects observed in the erythrocytes in the disease condition	[89]
Hypochromic anemia	*weißherbst*	Understanding the role of *ferropontin1*gene in the disease	[90]
Thalassemia	*zinfandel*	Providing a model for the studies related to thalassemia	[91,92]
Congenital dyserythropoietic anemia type II (HEMPAS)	*retsina*	Undertaking studies related to HEMPAS and understanding the role of certain genes related to it	[93]
Systemic mastocytosis (SM)	*c-KIT-D816V mutant*	Studying mast cell accumulation and its effect on multiple organs	[94]

clinical manifestations of DBA. Hypochromic anemia studies have been conducted in zebrafish models *weiβherbst* with a mutated *ferropontin1* gene [90] and *zinfandel* with mutant *globin* gene, which can also be useful for thalassemia studies [91,92]. The studies with *ferropontin1* in the *weiβherbst* model suggested that *ferropontin1* is required for intestinal iron transportation in zebrafish and that it could play a role in the export of iron from macrophages that is necessary for the recycling of iron from senescent erythrocytes, while also suggesting based on the results of the globin gene studies that teleosts have very well defined erythrocyte lineages that express various other globins as well, which can be used for generating more intriguing models of hemoglobin switching during the evolution of vertebras.

The study with Zebrafish mutant model *retsina* with a defect in the *erythroid anion exchanger 1/band3* gene has been used to study a rare blood disease called congenital dyserythropoietic anemia type II (HEMPAS) [93]. The results of the study showed that the retsina mutation is caused by defects in the zebrafish band 3 gene based on certain criteria derived from gene expression studies. A zebrafish transgenic model with the *c-KIT-D816V* mutation was recently developed to study systemic mastocytosis (SM) whose severity is characterized by mast cell accumulation in multiple organs [94]. It was understood from the study that the transgenic zebrafish model was capable of providing 'embryonic surrogate markers' having the potential of being used for future drug testing. It is also the first model for human mast cell disease. Studies quite recently led to the development and characterization of a zebrafish null mutant allele model for the *wasp* gene, represented in Fig. 5G and H, implicated in the study of Wiskott-Aldrich syndrome (WAS) and also X-linked severe congenital neutropenia (XNS) [95]. The study showed the importance of the *wasp* function and the potential of the model in testing with live imaging techniques the various effects of *wasp* mutations on the model system. It also linked the susceptibility of the model to bacterial infection as similar to those seen in patients with WAS and XNS. To facilitate studies of leukocyte adhesion deficiency (LAD), Rac2D57N zebrafish mutation models were developed [96] that suggested the role of *rac2* signaling in neutrophil retention by hematopoietic tissues. The results from this study helped provide a deeper understanding of *rac2* signaling which might be associated with its modulation leading to an increase in the mobilization of neutrophils since the role of *rac2* signaling is predominantly seen in neutrophils where they function by active retention of neutrophils thus limiting its mobility. Table 4 lists the various zebrafish models developed to investigate blood diseases.

Table 5
Limitations associated with disease modeling zebrafish.

Type of Limitations	Description	Reference
General Limitations	Presence of duplicate copies of mammalian genes despite the high similarity in the homology of zebrafish to rodents and human beings with the genomic duplication being events that are independent and continuous.	[108]
	Availability of genetically characterized strains of zebrafish is constrained due to its loss of fertility upon inbreeding and those that have been developed aren't easy to maintain.	[109]
	Divergence of a few functional genes due to genomic duplication limit the accuracy of disease modeling in zebrafish	[110]
	Zebrafish don't have sex chromosomes unlike humans and hence there is a difference in the sex ratio of the teleosts in the majority of research designs leading to varying levels of sexual dimorphism in comparison to mammals.	[6]
	Water-insoluble drug administration is a problem and requires the administration of the drug through various other mechanisms including the use of vehicles or techniques such as developing oral gavage or microinjections through the oesophagus.	[18]
	Despite having a good amount of physiological homology, the environmental conditioning between zebrafish and humans remains with the teleosts being maintained at about a temperature of 28 °C.	[5]
	Even though zebrafish have a blood-brain barrier (BBB) that is substantially alike to its human counterpart, due to the effect of differences between species, the action of drugs keeps changing due to the change of the BBB permeability causing a hindrance to drug testing. Similar effects due to species differences are also observed in cases of metabolism and thermoregulation. This accounts for one of the more serious limitations associated with the teleost models.	[18]
	The dosage cannot be easily translated directly from zebrafish into rodent or human doses and vice versa due to differences in the physiology between the species.	
Limitations in Bone Disease Modelling	Mineral ossification pathway is widely different in zebrafish in comparison to mammals especially terrestrial mammals due to the variance in the uptake and excretion of calcium.	[111]
	The development of the teleost skeletal system is prone to environmental influences which is not the case for most placental organisms.	[112]
Limitations in Cardiovascular Disease Modelling	Studying septal development including blood pressure and metabolism is a hindrance.	[113]
	There are differences in cardiac electrophysiology due to the variation in the cycling of calcium and ionic currents.	[114]
	There is a possibility of ventricular amputation due to the smaller size of zebrafish during ECG studies affecting the heart rate and the heart rate variability.	[115]
Limitations in Renal Disease Modelling	Disruption of the functionality of the glomerulus in the kidneys of zebrafish embryos causes the death of the embryos within a few days.	[116]
Limitations in Cancer Modelling	Most of the present zebrafish disease models for cancer are made by knocking out certain genes deviating from their corresponding syndromes which usually show missense mutations failing to truncate proteins. This doesn't allow for a proper investigation into the protein interactions or the genetic basis of the disease.	[117]
Limitations in Blood Disease Modelling	Studying lymphocyte subtypes and the biology of leukocytes is difficult due to the scarcity of well-characterized monoclonal antibodies acting on the leukocyte surface molecule.	[118]
	The difference in the morphology of some blood cells like erythrocytes and thrombocytes which are nucleated in zebrafish models might cause a hindrance in drawing parallels with humans and translating research.	

3.6. Other diseases

Apart from all the human disease studies previously discussed that are effective in zebrafish models, there are many other diseases for which models have been developed or are being developed to gain insight into the disease conditions. Some of these are diseases such as Duchene muscular dystrophy which is a fatal muscle-wasting disease that is being studied using the zebrafish model *dmd-MO* developed by knocking down Dystrophin using anti-sense morpholino oligomers (MO) [97], and retinal diseases in humans using the zebrafish model *no optokinetic response c* [98]. There have been studies that use zebrafish as model animals for understanding schizophrenia [99] and in various other addiction studies [100]. Recently, zebrafish models have been used to study autism spectrum disorders (ASD) [101] since zebrafish are considered highly social and for depression studies [102]. Zebrafish have also been used as models for many microgravity-related studies [103–105] in order to understand the effects of microgravity on humans as we take bold strides in space exploration over the next few decades.

4. Limitations associated with zebrafish disease modeling

Even though zebrafish disease models are very powerful models in terms of their potential towards building scientific knowledge, it doesn't come without a few of their inherent flaws. To fully comprehend the advantages of using zebrafish as a model organism in the future we must study and try to work around the limitations associated with zebrafish in general and while modeling. These hindrances have been highlighted in Table 5.

One of the other research areas which have gone back and forth over the years in agreeing to the utility of zebrafish in the field of research is neurosciences. This stems from the fact that, although there is a fair amount of conservation to the planning of the body and brain of vertebrates between zebrafish and humans, there is a lack of conservation in terms of brain anatomy that manifests itself in the form of an expanded telencephalon and a lack of prefrontal cortex [6]. In addition to that, the behavioral characteristics and the modeling of several developmental disorders are hindered as there is a lack of information about parental care among zebrafish. The difficulty in mapping CNS structures in zebrafish to draw parallels with mammals has also contributed to the modeling of complex brain diseases in the comparatively simple zebrafish neural system. These drawbacks however have not overshadowed the utility of the animal model in deriving the disease models as zebrafish have most of the major neurotransmitters, transporters, receptors, and a well-developed subcortical neural circuitry – allowing for the complex cognition functionality to be conserved with its subsequent human diseases of the CNS [106]. Thus, even though problems with the models remain in the field, it isn't ruled out as a future alternative for complex brain and neuron disease modeling with many zebrafish disease models for the brain and CNS being designed and available at present already for a wide range of diseases and disorders such as – anxiety, depression, pain, ADHD, epilepsy, neurodegeneration and many more [107].

However, all these limitations should not deter the field from gaining scientific traction, as although many of the aforementioned concerns regarding the zebrafish modeling are rational, most of them are relative and can be worked around with comparatively easier solutions and a probable scientific advancement in the future on the animal disease modeling front. Finding comparatively workable solutions for these limitations would aid the translational value gained from the studies conducted in zebrafish disease models.

5. Conclusion and future prospects

In this review, we have discussed the ever-expanding role of zebrafish models for human diseases in the avenue of research especially in the fields discussed earlier; helping us in understanding the cause, pathogenicity, mechanisms, and modes of infection, and figuring out the various molecular pathways associated with the disease condition allowing an effective research development into finding a cure for the disease by aiming for non-toxic but high efficacy drug designing. It also discusses the various zebrafish models that led to a successful as well as an effective study into several of the human diseases along with the general and disease modeling-specific limitations associated with zebrafish.

Although many of the diseases remain elusive, scientific pursuits toward understanding such diseases are gradually catching up with the creation of effective models that will revolutionize the medical field soon. Scientific research would always require animal models as they are integral to the understanding, development, characterization, reliability, and legitimacy of the hypothesized concepts and drug designs related to the disease study. The standout amongst these models will most likely be zebrafish owing to its genetic tractability and many more advantages related to it already discussed before in the introductory section of the review. With the advent of CRISPR technology, genetic manipulations have become easier and since such manipulations can easily be done in the zebrafish models to mimic human disease conditions, these teleost fish are becoming a major player in the myriad research fields.

One such prospective future initiation is studies related to microphthalmia, andophthalmia, and coloboma (MAC). Although zebrafish models for studying conditions have been around for more than a decade now [119], new zebrafish mutants discovered through various targeted mutagenesis and synthetic enhancer screens would guarantee the identification of new candidate genes for the condition, thereby improving our knowledge about eye developmental pathways while also shedding light on observed variabilities related to ocular malformation phenotypes [120,121]. Another fast-growing prospect already steadily compiling knowledge in its frontier is that of the effective use of zebrafish models to study neurodevelopmental diseases through the recognition of pathophysiologically relevant risk genes associated with them imparting translational relevancy [122]. Research has also begun dedicated to inflammasomes with the help of zebrafish models associated with the increasing number of autoinflammatory diseases which have thus far yielded a lot of knowledge related to disease conditions, but more perspective about them will be achieved in the future when cellular aspects will be recorded and therapeutic initiations are undertaken [123]. More prospects of the effectiveness of zebrafish

models in understanding human diseases will be seen in the fields of oncology, Alzheimer's disease, immunology, diabetic studies, regenerative medicine studies, aging-related studies, food safety, nutrigenomics, and its related disease studies.

These translational researches will pave the way hopefully for a paradigm shift in medical research and add therapeutic values to the product of those researches. The teleost animal model continues showing vast potential in terms of its translational potential which can probably be capitalized on in the near future to develop probable novel therapeutic interventions.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Copyright permission obtained for used figures and images accordingly.

Data search strategy

The articles presented and cited in the review have been searched in PubMed, Google Scholar, ZFIN, Scopus engines. The articles were screened using the keywords "zebrafish" in addition to the name of the broad category of diseases. Both review and research papers were considered for studying the work associated with zebrafish over the span of the last two decades. The references in previously published reviews were also screened, searched and read before revising the articles in this review.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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