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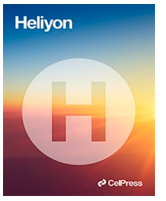

Review article

A review on current advancement in zebrafish models to study chronic inflammatory diseases and their therapeutic targets

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ABSTRACT

Chronic inflammatory diseases are caused due to prolonged inflammation at a specific site of the body. Among other inflammatory diseases, bacterial meningitis, chronic obstructive pulmonary disease (COPD), atherosclerosis and inflammatory bowel diseases (IBD) are primarily focused on because of their adverse effects and fatality rates around the globe in recent times. In order to come up with novel strategies to eradicate these diseases, a clear understanding of the mechanisms of the diseases is needed. Similarly, detailed insight into the mechanisms of commercially available drugs and potent lead compounds from natural sources are also important to establish efficient therapeutic effects. Zebrafish is widely accepted as a model to study drug toxicity and the pharmacokinetic effects of the drug. Moreover, researchers use various inducers to trigger inflammatory cascades and stimulate physiological changes in zebrafish. The effect of these inducers contrasts with the type of zebrafish used in the investigation. Hence, a thorough analysis is required to study the current advancements in the zebrafish model for chronic inflammatory disease suppression. This review presents the most common inflammatory diseases, commercially available drugs, novel therapeutics, and their mechanisms of action for disease suppression. The review also provides a detailed description of various zebrafish models for these diseases. Finally, the future prospects and challenges for the same are described, which can help the researchers understand the potency of the zebrafish model and its further exploration for disease attenuation.

1. Introduction

Inflammation is instigated as a defense mechanism stimulated by the body to fight against harmful pathogens, damaged tissue, or any noxious chemicals thereby it promotes the healing of the injured tissues [1]. The rapid inflammation that occurs for a short period of time is called acute inflammation which, when uncontrolled becomes chronic. The brain experiences various inflammatory responses, causing diseases like meningitis. Unbalanced defense reactions in the brain might make it unable to control inflammation leading to severe damage. This inflammation results in vasculitis, septic thrombosis, and tissue injury [2]. Due to the underdeveloped immune system, infants, and children below the age of 10 are more susceptible to bacterial meningitis than adults. Pneumococcal meningitis has a 10–30 % mortality rate and the lowest is meningococcal with a 4–5% mortality rate [3]. Similarly, inflammation in the lungs caused by various environmental pollutants and harmful pathogens leads to chronic obstructive pulmonary disease (COPD),

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with cigarette smoke being the hallmark feature of the disease's progression. Several studies have reported that infection and inflammation play a major role in coronary heart disease [4]. Atherosclerosis causes the accumulation of lymphocytes and macrophages in the vessels leading to a high concentration of C-reactive protein. The C-reactive protein acts as an inflammatory marker which helps to subdue the disease. Furthermore, other inflammatory molecular targets are released by macrophages and foam cells such as reactive oxygen species, interleukins, interferons, chemokines, and tumor necrosis factors which are involved in the elevation of the disease [5]. The inflammatory signals along with risk factors leading to atherosclerosis, alteration of lifestyle is another reason behind elevated atherosclerosis cases in young patients [6]. Another major inflammatory condition is bowel disease comprised of Crohn's disease and ulcerative colitis where the inflammation is associated with the small intestinal and colon. The onset of the disease leads to chronic swelling and redness in the intestinal tract with severe pain [7]. Various anti-inflammatory drugs such as corticosteroids, non-steroidal drugs, sulfasalazine, and opioids, are prescribed to alleviate the symptoms of the disease [8]. Although, due to various risk factors associated with these drugs, the administrations cannot be given for a prolonged period. Hence, novel drugs need to be studied with improved bioactivities to suppress the disease symptoms. *In vivo* models are best suited to investigate the efficacy of lead compounds prior to any pre-clinical trials. Hence, an ideal *in vivo* model that is cost effective, reproducible, and genetically similar to human should be available in order to study the same.

Zebrafish (*Danio rerio*), a teleost has emerged as an ideal candidate for modelling chronic inflammatory-related diseases in recent years and their role in the discovery of novel drugs is also established [9,10]. Zebrafish have the ability to regenerate, which makes them an excellent model for studying tissue repair and regeneration [11]. Zebrafish and human physiology exhibit similarities during the developmental stage, since they share evolutionarily conserved molecular and developmental landmarks [12]. Additional justifications for utilizing zebrafish as a model include its genetic resemblance to humans, brief lifespan, and analogous immunoinflammatory reactions in the presence of diseases [13,14]. Zebrafish and mammals share similarities in terms of their possession of an innate immune system, pattern recognition receptors, and complement proteins. Despite having fewer recognition receptors than mammals, zebrafish exhibit conserved functioning and the major response they create aligns with the human inflammatory response after pathogenic attacks [15]. Despite the production of B and T cells, zebrafish have less developed adaptive immunity compared to mammals. This is mostly owing to the lack of well-formed thymus, bone marrow, and lymph nodes [16]. However, both zebrafish and mammals exhibit comparable immunoinflammatory responses to infections and diseases through cytokine overexpression, making them suitable models for studying inflammatory diseases [17]. The immunological response in zebrafish involves the recruitment of leukocytes and the infiltration of neutrophils, which is comparable to the process observed in humans during inflammatory circumstances. The leukocyte migration in fish is from head, and kidney but in humans it is from the bone marrow [18]. While mammals show limited regenerative capacity, inflammation in zebrafish activates the neurogenesis and tissue regenerative capacity [11]. Hence, through genetic manipulation, chemical induction, and wound formation various model are developed in zebrafish to examine different aspects of the disease prognosis and the effects of therapeutics on suppressing the activated response [19,20]. Onset of diseases, dietary factors, genetic manipulations, therapeutic effects of anti-inflammatory drugs and mechanisms of drug delivery can be studied through these models [10,21,22]. Fig. 1 illustrates various inducers used for the induction of chronic inflammatory diseases

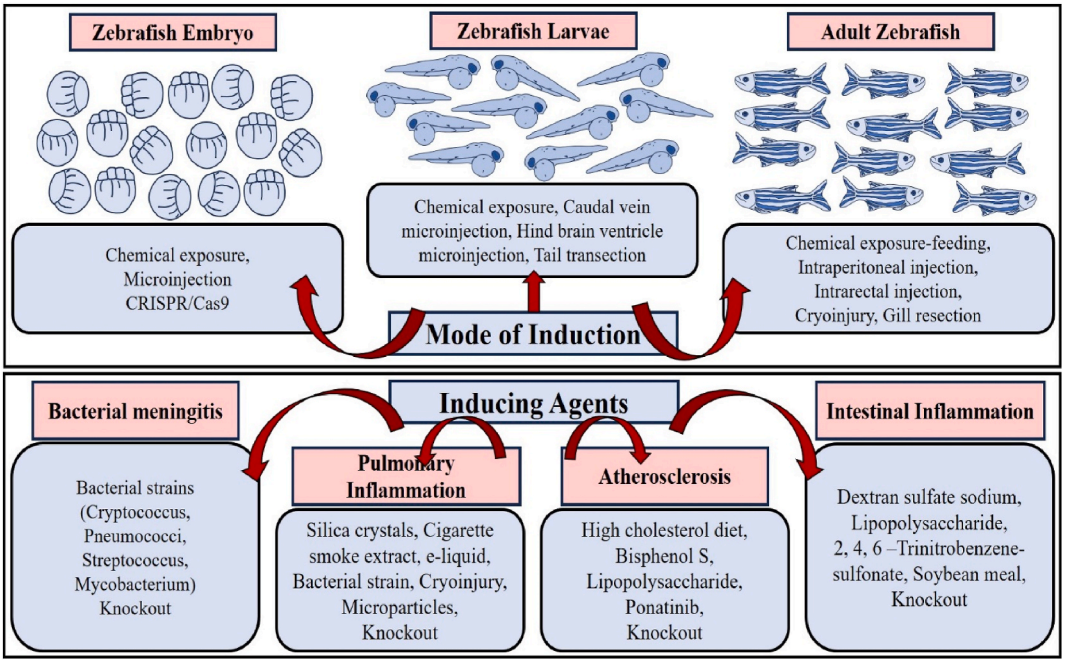

Fig. 1. Graphical illustration for the modelling of inflammatory diseases (Bacterial meningitis, Pulmonary inflammation, Atherosclerosis, Intestinal Inflammation) in various stages of zebrafish.

in the zebrafish model and the type of induction in different stages of zebrafish. In this review, risk factors associated with inflammatory diseases are briefly discussed. Current advancements in the development of zebrafish models for chronic inflammatory diseases are disclosed. Further, the challenges and future prospects of zebrafish model development for effective drug screening and disease management are also discussed.

2. Chronic inflammatory diseases: risk factors, therapeutic progression and their mechanism of action

2.1. Bacterial meningitis

Meningitis is commonly caused by bacterial and viral infections, but it may also rarely occur due to fungal infections. Bacteria-infected meninges are fatal and constitute a high mortality rate. There are 3 major sources of bacterial meningitis, *Haemophilus influenza*-type B (haemophilus meningitis), *Neisseria meningitidis* (meningococcal meningitis), and *Streptococcus pneumoniae* (pneumococcal meningitis). These sources contribute to 95 % of bacterial meningitis cases. Their mode of infection can occur through open tissue injury, ear sinuses, or hematogenous dissemination (bloodstream) [23]. In certain cases of tuberculosis, patients with chronic exposure to *Mycobacterium tuberculosis* in the brain and spine reported infection with tuberculous meningitis [24]. Haemophilus meningitis and pneumococcal meningitis are most common in children and infants; however, cases of haemophilus meningitis have decreased in infants since 1980 [25]. Meningococcal meningitis occurs in children of the age group 2–18 years and rarely in adults >50 years. Although, long term neurological disorders have been observed in the survivors [2].

Studies have revealed that meningitis is an inflammation of the meninges in the brain and its subarachnoid space that can also include the cortex and parenchyma portion owing to their subsequent anatomical placement between the cerebrospinal fluid and the brain. Pathogens invading through the bloodstream are the major route of entry to the subarachnoid space [26]. The pathogen colonization occurs in the epithelial tissues of the respiratory, gastrointestinal, or lower genital tract. Once inside the bloodstream, the pathogen, with the help of its capsular polysaccharides, can survive the host defense mechanisms [27]. After surviving the defense mechanisms, the pathogen develops a variety of methods to uptake iron from the host, which in turn helps in replication and its metabolism. Prolonged high levels of bacteremia are shown to favor bacterial penetration into the subarachnoid space which is the entryway to the central nervous system [28,29]. The inflammatory reaction assumes an imperative part in infection pathogenesis, with bacterial mixes perceived by brain-inhabitant invulnerable cells capable of selecting myeloid differentiation factor 88 and translocation of NF-κB, which induces inflammatory mediator production. A one-way treatment capable of decreasing both inflammation and hippocampal apoptosis could potentially improve outcomes in children with *S. pneumoniae* meningitis [2,30]. Early antibiotic treatments are the prescribed method for bacterial meningitis, but due to multidrug resistant bacteria the effectiveness of the antibiotics is reduced and the demands for alternative methods of treatment are increasing rapidly.

The studies on adjunctive therapeutic strategies are still in their developmental stages. Some commonly used drugs are amoxicillin/ampicillin, ketorolac, etodolac, fluoroquinolones, and tigecycline [31,32]. Adjunctive dexamethasone therapy has proven that it can suppress subarachnoid space inflammation and reduce the risk of hearing impairment in children [33]. Daptomycin is a lipopeptide with a cyclic structure that is active against gram-positive bacteria [34]. Among other drugs, cefepime is considered the second-line treatment for *H. influenzae* meningitis and for post-neurosurgical meningitis patients, it is used as the first-line treatment [35]. It is the fourth generation of cephalosporins that helps destabilize the lactamase structures in bacteria. Cefepime has the ability to bind to penicillin binding proteins present in bacteria. This binding stops the last step of transpeptidation that happens during the making of the peptidoglycan wall in bacteria cell walls. The inhibited bacterial cell wall synthesis leads to the lysis of bacteria. The bactericidal property of cefepime is strengthened due to the presence of a zwitterionic charge in the methyl pyrrolidinium group present in its structure [36,37]. Cefepime can easily penetrate the outer membrane of the Gram-negative bacteria because cefepime has a neutral charge, thereby helping for easy and rapid penetration [38]. Leukocytes also play an important role in inflammatory responses during bacterial infections where the pattern recognition receptors penetrate the blood brain barrier activating endothelial cells lining the blood vessels. Leukocytes are recruited on the endothelial lining where they migrate to central nervous system by diapedesis and release pro-inflammatory cytokines. Leukocyte inhibitors and anti-adhesion molecule antibodies are studied which may be a viable solution for the suppression of inflammation during microbial infections [39]. Apart from these chemical-based drugs, natural derivatives are also studied which can help attenuate the onset of meningitis associated inflammation.

2.2. Pulmonary inflammation

COPD, a prevalent lung disease, is described by airflow obstruction to the lungs which interferes with regular breathing patterns [40]. Due to the long-term exposure to various particles and lethal gases, abnormal inflammation is caused in the lungs, leading to breathing complications. Cigarette smoking and genetic abnormalities are risk factors for COPD. Among these, cigarette smoking is the major risk factor [41]. The duration of cigarette smoke exposure to the lungs is the factor that is going to determine the severity of airflow obstruction. These factors lead to the damage of lung tissue by causing an augmented inflammatory response. The two major forms of COPD include chronic bronchitis and emphysema. Chronic bronchitis is caused by inflammation in the epithelium of mucus-producing glands, which leads to increased levels of mucus secretion. Emphysema is a condition in which the distal airspace beyond the terminal bronchiole gets permanently enlarged [42]. Another form of COPD is small airway disease, which is caused by peribronchial fibrosis and inflammation. The major cause of emphysema is the destruction of walls of the airway in lungs. Since COPD was found to be the fifth leading cause of death in 2002 and it is expected to be the third leading cause of death by 2030 [43]. It is important to completely understand the mechanism of the disease and eradicate it at the earliest.

The innate as well as adaptive immune systems play a major role in pathogenesis of COPD. The increased number of inflammatory cells in the lungs is evident at the onset of the disease. These inflammatory cells later release a vast spectrum of mediators and cytokines that participate in the pathogenesis of disease [44]. During the innate immune response, we observe neutrophils and macrophages which increase the production of proteases, anti-proteases causing activation of inflammatory signals, excess mucus secretion, and pulmonary congestions, ciliary dysfunction [45]. The activation of the inflammatory cascade also results in the secretion of matrix metalloproteinases (MMP) like MMP-8, MMP-9, and MMP-12 [46]. Various pro-inflammatory cytokines which are secreted in increased quantities are tumor necrosis factor α, interleukin 1β. The transcription factor NF-κB controls the indicated inflammatory mediators [47]. CD4 and CD8 of T -lymphocytes and B-lymphocytes are observed during the adaptive immune response. The most prevalent cells available are CD8 cytotoxic T cells, which cause the alveolar wall destruction [48]. Airflow obstruction and hyper-inflation are also some of the pathological changes observed. The airway obstruction is caused due to the loss of lung elastic recoil which is because of alveolar wall destruction. Treatment focuses on inhibiting inflammatory mediators. TNF-α receptor is the one which is crucial in establishing emphysema in the lungs [49].

The frequently focused therapeutic targets are phosphodiesterase-4 inhibitors, adenosine A2a-receptor agonists, and adhesion molecule interacting drugs [50]. Phosphodiesterase-3 and phosphodiesterase-4 are usually targeted receptors in COPD treatment [51]. Theophylline (dimethylxanthine) is a bronchodilator that acts as an inhibitor of phosphodiesterase 3. Phosphodiesterase is an isoenzyme that is prevalent in inflammatory cells and plays a key role in COPD pathogenesis. Phosphodiesterase-4 regulates cAMP in smooth muscle cells which in elevated conditions promote tissue damage and airway obstruction. Theophylline is commonly used as an anti-inflammatory therapeutic. The main reason theophylline reduces inflammation is that it stops phosphodiesterase-4 and histone deacetylase-2 from activation [52]. We can inhibit the discharge of inflammatory mediators from alveolar macrophages by inhibiting phosphodiesterase-4. The high concentration of theophylline increases the release of interleukin 10, which has anti-inflammatory effects. Theophylline also reduces the expression of the inflammatory gene by preventing the NF-κB translocation into the nucleus [53]. The reduced activity of histone deacetylase-2 in COPD cells is restored to normal by theophylline, which is done by inhibiting phosphoinositide 3-kinase δ. This phenomenon reduces the corticosteroid resistance in COPD patients [54]. The suppression of inflammatory genes like granulocyte macrophage-colony stimulating factor and interleukin-8 occurs by the activation of histone deacetylase by low concentrations of theophylline [55]. This histone deacetylase helps in the deacetylation of core histones. The anti-inflammatory effect of theophylline is found because it has the ability to suppress the proliferation of $CD4^+$ and $CD8^+$ lymphocytes [56]. However, there are some common side effects, like increased secretion of acid, nausea, and vomiting due to phosphodiesterase inhibition. Other side effects include cardiac arrhythmias and convulsions which occur at high concentrations of drug exposure [57]. Hence, other chemical drugs have also been adapted to treat the pulmonary associated inflammation. Various naturally derived therapeutic targets are also currently being studied to suppress the symptoms of pulmonary inflammation [58–62].

2.3. Atherosclerosis

Among several diseases, cardiovascular diseases are a major cause of death and result in extreme disabilities in many countries. Although there are several primary and secondary level preventive measures to control cardiovascular diseases like smoking, cholesterol levels, diabetes, and obesity, the death rate due to cardiovascular diseases has influenced the world to look for an alternate approach to prevent it [63]. Atherosclerosis is a progressive disease of the arteries that can be distinguished by atherosclerotic plaque which is caused by lipid accumulation, extracellular matrix remodeling and develops into lesions due to the presence of macrophages and monocytes. According to studies, the process of lipid metabolism is directly impacted by gut microbiota [64]. To decrease cholesterol levels through absorption, it must undergo conversion into bile acids. However, this process is hindered by specific bacteria, resulting in the buildup of lipids in the liver and gallbladder [65]. Therefore, by altering the host's lipid metabolic process, gut bacteria contribute to the development of inflammatory plaque in atherosclerosis [66]. Additionally, large, and medium elastic arteries typically exhibit these lesions, leading to heart ischemia and stroke. The formation of lesions is accompanied by an inflammatory response from the host causing the release of proinflammatory cytokines [67]. Inflammation in the arterial region can cause plaque rupture and thrombosis, which eventually cause myocardial infarction. This inflammation can be caused by the direct infection of specific microbes such as *Chlamydia pneumoniae, Heliobacter pylori,* and Cytomegalovirus in the carotid artery region [68,69]. Inflammation and heart failure are a result of each other, the chronic inflammation stage can be prevented with early diagnosis, further preventing heart failure [70]. Moving and multiplying smooth muscle cells over and over again in the arteries creates fibrous tissue, which puts stress on the heart's ability to widen and change the speed of blood flow to it [67]. Despite improving lifestyle changes, reducing lower plasma cholesterol concentration levels, and improving pharmacological approaches towards cardiovascular diseases, it still prevails as a major cause of death in several countries [71].

Inflammatory response occurs in 4 stages: 1) involvement of exogenous (pathogen-associated molecular pattern molecules, non-microbial inducers) inflammatory inducers such as bacterial cell wall components: lipopolysaccharides, peptidoglycans, microbial DNA, viral glycoproteins and endogenous (damage-associated molecular pattern molecules, Extra-cellular matrix derived products) inflammatory inducers such as heat shock proteins, mitochondrial DNA, elastin, fibronectin, oxidized low-density lipoproteins, matrix metalloproteases; 2) The sensory signals which help in detecting the inducers-pattern recognition receptors, such as AIM-2 type receptors, Toll-like receptors, Nod-like receptors; 3) overproduction of inflammatory mediators TNF-α, IL-6, IL-1β; and 4) communication to the target site that is affected by the mediators [1]. Atherosclerosis can be influenced by certain risk factors that trigger release of cytokines (TNF-α, IL-6, and IL-1β) from monocytes of the host immune system [5]. In response to the released cytokines, leucocytes and platelets are recruited by adhesion molecules, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 to the site of inflammation for enhanced attachment of leucocytes [63,72]. The release of neutrophils and platelets is stimulated by IL-6

from the bone marrow as a signal to a chronic inflammatory reaction. The increased synthesis of hepatic protein due to IL-6 and other cytokines causes the release of C-reactive protein, serum amyloid A, and fibrinogen. They are the traditional blood markers in which the measurement of C-reactive protein and fibrinogen levels is done in the early stages of acute tissue injury [73,74]. Simultaneously, the monocyte-derived macrophages and foam cells lead to increased lipid accumulation in the later stages of atherosclerosis. Further, the cytokines over-production, and matrix deterioration leads to the development of thrombus [75].

Low-density lipoproteins play a role in activating both innate and adaptive immunity [76], which is why inflammatory therapy for atherosclerosis is considered effective. The targets involved in the treatment of atherosclerosis include angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, anticoagulants, and platelet inhibitors [77]. The ACE inhibitors widen or dilate the blood vessels, thereby helps to increase the blood flow which is specified. ACE converts angiotensin I to angiotensin II increasing blood pressure. The binding of angiotensin II stimulates aldosterone, which increases blood pressure due to the kidney's reabsorption of water and sodium instead of potassium [78]. Captopril, an ACE inhibitor, inhibits the conversion of angiotensin I to angiotensin II, thereby causing a decrease in aldosterone and vasodilation. Captopril modulates the level of dendritic cells in atherosclerotic lesions. It has the ability to arrest the maturation of dendritic cells and thereby, protect its anti-atherosclerotic properties [79]. In addition to dendritic cells, macrophages and monocytes are essential contributors to the regulation of inflammatory signalling pathways involved in the development of cholesterol and fat-based plaques. The macrophages phagocytose the LDL cholesterol and then differentiate into foam cells, hence enhancing the production of CCL-2 and CCL-5, as well as promoting cell migration [80]. Statins have been proposed to mitigate foam cell production and regulate macrophage function by facilitating cholesterol efflux. In addition, the utilisation of PCSK9 inhibitors and PPARγ agonists has been found to contribute to the enhancement of mitochondrial function and plaque stability [81]. On the other hand, adhesion molecules such selectins, ICAM-2, and VCAM-1 facilitate the attraction of white blood cells to the artery wall, resulting in inflammation and expanding. Recent research has demonstrated the efficacy of monoclonal antibodies and small molecule inhibitors in mitigating the recruitment of leukocytes, hence leading to a reduction in inflammation [82]. In addition to these factors, oxidative stress is a major contributor to the worsening of inflammation and endothelial dysfunction in the arterial walls. Oxidative stress arises from the generation of reactive oxygen species by different cells. The neutralization of reactive species can be facilitated by several formulations that incorporate vitamins and bioactive peptides. Various oligopeptides obtained from marine sources have shown enhanced inhibition when compared with chemical-based therapeutics [61]. These natural compounds can be explored further in detail to understand the therapeutic mechanism of action *in vivo*.

2.4. Intestinal inflammation

The disorder due to chronic inflammation observed in the gastrointestinal tract is called as IBD. More than 3 million people are affected by IBD globally with the major incidence seen in North America and European countries [83]. IBD is classified into two types of diseases, namely, ulcerative colitis and Crohn's disease. In ulcerative colitis, inflammation is found in the innermost layer of the lining of the colon, whereas in Crohn's disease, inflammation is observed as patches in multiple layers of the gastrointestinal tract. The gastrointestinal tract is a hub of bacterial flora with approximately 300–500 species of bacteria [84]. The protection of the host from noxious pathogens is provided by the inner cell lining of the intestine. Moreover, the complex interactions between these microbes also occur here. These interactions are balanced by the innate and acquired immune systems of the intestine under homeostasis. The imbalance in the microbiome interaction leads to IBD.

Understanding the coaction between environmental, genetic, intestinal barrier, and immune response factors is crucial for studying the mechanisms related to the pathogenesis of IBD [85]. Environmental factors are found to play a demanding role in the occurrence and progression of IBD. These factors disrupt the intestinal flora and its homeostasis. The recognized factors are lifestyle events, diet, smoking, use of medications, infections, and air pollution [86]. The diet rich in fiber lowers the likelihood of Crohn's disease. This is because the intestinal microbiome metabolizes the fiber into light chain fatty acids, which have anti-inflammatory property. Medications like antibiotics, anticontraceptive, and nonsteroidal anti-inflammatory drugs increase the possibility of IBD [87]. Understanding genetic factors is crucial in IBD, as genome-wide association studies indicate that various genetic polymorphisms cause IBD [88]. Due to various environmental factors, the intestinal bacterial levels that metabolize light chain fatty acids get highly reduced. Nucleotide-binding oligomerization domains containing protein 1 were recognized in IBD pathogenesis [89]. Mutation in this gene as well as in the autophagy related 16-like 1 gene is also important in the pathogenicity of the disease [90]. In the case of Crohn's disease, the T-helper-1 cells are responsible for the pathogenesis, whereas for ulcerative colitis, it is T-helper-2 cells [91]. Both innate and acquired immune responses occur in IBD pathogenesis. The innate immune system guards the host through pattern recognition of pathogens. The adaptive immune system provides a highly specific protection to hosts. The innate immune cells as well as intestinal epithelial cells are present in the intestinal barrier. The goblet cells, paneth cells, and M cells, maintain an equilibrium between the lumen and mucosa, thereby protecting them from an inflammatory response. The mucus matrix is created by goblet cells which help in providing defense to the intestine [92]. In case of adaptive immunity, antigen presenting cells such as macrophages and dendritic cells generate signals which release pro-inflammatory as well as anti-inflammatory cytokines. These cytokines provide support for the migration of leukocytes to the location where inflammation occurs, and thus help in the progression of IBD.

The treatment for IBD is done using various anti-inflammatory drugs such as corticosteroids and amino salicylates. These conventional drugs are considered as the first-line treatment for IBD. Apart from that, monoclonal antibodies with *anti*-TNF as well as anti-adhesion properties are also in use [93]. When conventional drugs such as amino salicylate fail to cure the disease, anti-tumor necrosis factor therapy comes into play [94]. The goal of the drug is to reduce inflammation as well as repair the mucosa layer. IBD patients primarily receive prescriptions for these drugs. Low doses of anti-inflammatory drugs do not pose many side effects, but regular or high

doses might show abnormal effects in patients [95]. Among other drugs, 5-aminosalicylic acid and its derivatives act as front-line therapy for ulcerative colitis [96]. Certain nuclear receptors are involved in the activation of inflammation suppressing responses. One such receptor is γ-form peroxisome proliferator-activated receptor (PPAR-γ) which regulates the gene expression and cellular processes of during inflammation and metabolism. During intestinal inflammation, activation of PPAR-γ promotes mucin and protein expression at tight junctions which maintains the epithelial integrity. Adipose tissue and colon epithelium express the PPAR-γ at a higher level than the small intestine [97]. 5-aminosalicylic acid creates a conformational change in PPAR-γ and due to this co-activator DRIP is recruited and thereby, retinoid X receptor and PPAR-γ form a heterodimer. This leads to the activation of PPAR-γ response elements. PPAR-γ directly interacts with β-catenin in Wnt/β-catenin signaling pathway, wherein β-catenin is attached to the axin/GSK3b/APC complex. As a result of this interaction, β-catenin gets degraded; thereby, it does not get localized to nucleus. This interaction reduces the transcriptional activity of NF-κB. It is found that 5-aminosalicylic acid has the ability to activate PPAR-γ and thus helps in treating IBD [98]. The use of 5-aminosalicylic acid is found to be ineffective during the preoperative cases [99]. Researchers are currently studying a variety of natural therapeutics to suppress intestinal inflammation. Some of the common lead compounds includes monoterpenes, bioactive peptides, sulphated oligosaccharides [100–102].

3. Zebrafish models to investigate therapeutics against chronic inflammatory diseases

The use of animal models is an important instrument for gaining a clear understanding of the pathogenesis of the disease as well as to discover novel therapeutics for the treatment of the disease. Moreover, the models considered for the study should develop the disease within a short duration of time. There are several studies conducted using mice, rabbit, guinea pig models for testing. These animal models are well established; however, they need high maintenance facilities. Zebrafish, being the fast-emerging and easy to maintain animal model, acts as an attractive alternative for studies related to inflammatory diseases provided it has a major advantage of optical transparency [103]. Apart from that, the high similarity of inflammatory genes to mammals plays a key role in investigating the mechanism of inflammatory diseases. The inflammatory signalling mechanisms of zebrafish also showed similarity to mammals and thus are found to be validated as an ideal model for inflammation-related disease analysis [14]. Various disease model of zebrafish associated with inflammation and their current progressions are detailed in further sections.

3.1. *Bacterial meningitis zebrafish model*

Induction of infection of *S. pneumoniae* in a zebrafish embryo model in a proper dose-dependent manner has been performed and the role of clearance of bacteria from the host by its immune cells has been investigated recently [104]. It also reported the role of C-reactive protein in defense against the bacteria. Moreover, the attenuation of various virulence factors of pneumococci such as capsule, pneumolysin, autolysin proved to be avirulent in the zebrafish embryo [105]. In another model of pneumococcal meningitis,

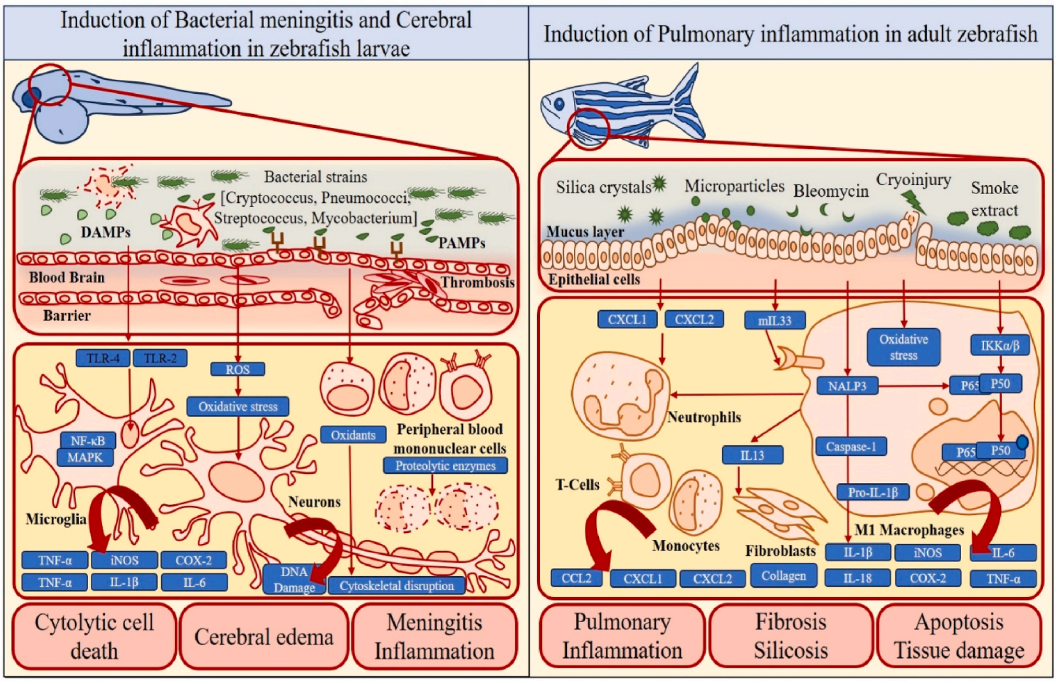

Fig. 2. Diagrammatic representation of molecular induction of bacterial meningitis, cerebral inflammation and pulmonary inflammation in zebrafish model.

the host-microbe interaction is inspected with the help of a transgenic zebrafish embryo lines. Neutrophils were mostly found due to infection of *S. pneumoniae* in the subarachnoid space. Comparing the pneumolysin-deficient mutant strain in the hindbrain ventricles with wild-type strains, growth attenuation is found in the subarachnoid space and the migration of bacteria to brain is also attenuated in the mutant strains [106]. Adult zebrafish model for pneumococcal meningitis has been evolved by the injection of pneumococcal strain TIGR4, which caused infection by its infiltration of the blood–brain barrier and induced disease progression. Moreover, infection with mutant bacteria has no virulent component in them attenuated in the disease model [107].

The tuberculous meningitis zebrafish model is developed to understand the development of meningitis in the primary stage itself, so that early detection of the disease can be done to eradicate it. The *Mycobacterium marinum* infection on both embryos and larvae of zebrafish was done by both local and systemic methods of infection at different inoculation sites such as parenchyma, hindbrain ventricle and caudal vein of embryos and microinjection of the heart of larvae showed the formation of early granuloma development in the parenchyma of the brain [108]. The first *Streptococcus agalactiae* meningitis found in newborns has been demonstrated by its infection in an adult zebrafish model proving the penetration of group B streptococcus into the central nervous system and causing inflammation in the brain. This model also concluded that β-hemolysin and the polysaccharide capsule are the crucial virulence factors

Table 1
Recent investigations on zebrafish models for bacterial meningitis and cerebral infection.

Disease Model	Zebrafish stage and infecting agent	Objective of the model	Prominent results	References
Zebrafish model of Cryptococcal meningitis	Zebrafish larvae infected with *Cryptococcus neoformans*	Investigate pathogenesis of cryptococcal meningitis and identify potential targets for the treatment	Vasodilation and constriction in the cranial vasculature with an impact on vessel wall permeability.	[111]
Zebrafish model of Pneumococcal meningitis	Casper zebrafish larvae injected with pneumococci producing pneumolysin	Study the effect of Pneumolysin in pathogenesis pneumococcal infection	Upregulation of genes involved in innate immune signaling, TLR signaling pathway, and NOD-like receptor signaling pathway.	[112]
Zebrafish model of Meningococcal infection	Zebrafish embryos infected with *Neisseria meningitidis*	Study the effect of capsule polysaccharide structure on host-pathogen interaction	Neutrophil depletion was observed after infection with encapsulated H44/76, but not with its non-encapsulated variant HB-1.	[113]
Zebrafish model of Tubercular meningitis	Zebrafish embryos infected with *Mycobacterium marinum*	Elucidate Tubercular meningitis pathogenesis	*M. marinum* can invade microglia and replicate in microglia which promote the secretion of pro-inflammatory cytokines.	[110]
Zebrafish model of Pneumococcal meningitis	Zebrafish embryos infected with *Streptococcus pneumoniae*	Investigation of early host-microbe interaction	Focal clogging of the pneumococci in the blood vessels and migration of bacteria through the blood-brain barrier into the subarachnoid space.	[106]
Zebrafish Model of Cryptococcal Infection	Zebrafish larvae microinjected with cryptococcal cells via caudal vein	To study pathogenesis from earliest interactions	Neutrophils are responsible for early infection and eliminating secondary fungemia. Macrophages are the primary host cells harbouring cryptococcus.	[114]
Zebrafish Model of Cryptococcal Infection	Zebrafish embryo and larvae injected with *C. neoformans* into the caudal vein	Investigate cryptococcal pathogenesis, high-throughput screening of mutants	Colonization of cranial vasculature, brain ventricles and brain tissue by 4-day post-injection.	[115]
Zebrafish model of Tuberculosis	Adult zebrafish infected intraperitoneally with *M. marinum*	Investigate the role off Furin in regulation of host response against infection	Silencing Furin genes reduced the survival of *M. marinum*-infected zebrafish embryos. Infected mutants resulted in elevated pro-inflammatory cytokine levels.	[116]
Zebrafish model of Streptococcus infection	Zebrafish larvae infected with *Streptococcus agalactiae*	To study bacterial and host factors that contribute to the disease progression.	Infection resulted in dose dependent larval death. ST-17 strain was observed as the most virulent.	[117]
Zebrafish model of Tuberculous meningitis	Zebrafish embryos infected with *Mycobacterium marinum*	Model to study granuloma formation in the brain	Infiltration of brain tissue, bacteria able to cross blood-brain barrier with high efficiency	[108]
Zebrafish model of Pneumococcal infection	Rag1 mutant zebrafish infected with *Streptococcus pneumoniae*	To study the immune response from pneumococcal infection	Intramuscular and intraperitoneal administration of pneumococcal strain TIGR4 cause dose-dependent infection in zebrafish	[107]
Zebrafish model of infection	Intraperitoneal injection of bacterial strains in adult zebrafish	To study the immunological role of cinnamaldehyde encapsulated in liposomes	Immersion treatment of liposome-encapsulated cinnamaldehyde reduced the inflammatory response. Moreover, it also enhances survival rate reducing bacterial growth.	[118]
Zebrafish model of Bacterial meningitis	Adult zebrafish infected with *Streptococcus agalactiae*	Study the pathogenesis of invasive group B streptococcus disease	The group B streptococcus is able to replicate zebrafish bloodstream and penetrating the blood–brain barrier	[109]
Zebrafish model of Tuberculosis	Adult zebrafish infected intraperitoneally with *M. marinum*	Investigate the effect of gamma radiation in reactivation of infection	Gamma radiation exposure transiently depletes granulocytes and lymphocyte pools while leads to 88 % mortality in four weeks.	[119]
Zebrafish model of Streptococcus infection	Adult zebrafish injected intraperitoneally or intramuscularly with bacterial suspension	Investigate the effects of streptococcal infection in zebrafish organs	More inflammatory cells accumulated at the site of infection. Numerous exudative inflammatory cells were present at the necrotic regions.	[120]

Table 2
Recent studies on zebrafish models for pulmonary inflammation.

Disease Model	Zebrafish stage and infecting agent	Objective of the model	Prominent results	References
Zebrafish model of silicosis	Injection of silica crystal in hindbrain ventricle of zebrafish embryo	Study the molecular mechanism in activation of immune system by silica crystals	Nlrp3 inflammasome regulated the induced inflammation and pyroptotic cell death.	[122]
Zebrafish model of pulmonary inflammation	Adult zebrafish exposed to cigarette smoke extract concentration.	Study the effect of betanin on suppression of pulmonary inflammation	LC_{50} for of cigarette smoke extract was observed to be 0.6 cigarette/litre. Nitric oxide, reactive oxygen species and myeloperoxidase enzyme content was maximum in induced fish which was reduced upon treatment with betanin.	[123]
Zebrafish model of mucosal inflammation and oxidative stress	Adult zebrafish exposed to cigarette smoke extract concentration.	Study the effect of quinine in ameliorating pulmonary inflammation	Exposure of cigarette smoke extract significantly increased the levels of reactive oxygen species, nitric oxide, myeloperoxidase and cytokines. Increased neutrophil accumulation and damages gill filaments in exposed group. Quinine reduced the inflammation at 15 mg/kg concentration.	[127]
Zebrafish model of lung inflammation	Exposure of zebrafish embryos with e-liquid	Employment of 2-stage screening platform for pulmonary inflammation through zebrafish embryo and C57BL/6J mice models.	E-liquid induce inflammatory response in zebrafish model such as neutrophil migration which is a key hallmark of pro-inflammatory response.	[128]
Zebrafish model for macrophage activation	Zebrafish larvae tail transected to develop a wound	Study the effect of Qinggan Yin formula on suppression of inflammation and its molecular mechanism	Treatment of Qinggan Yin formula reversed the macrophage migration toward the injury site in zebrafish model	[129]
Zebrafish model of silicosis	Injection of silica crystal in hindbrain ventricle of zebrafish embryo	Study the anti-inflammatory and anti-fibrotic effects of VX-765 and pirfenidone combination.	Induction leads to activation of both local and systemic immune responses through TLR and inflammasome dependent signaling pathways. Combination of VX-765 and pirfenidone alleviated both inflammation and fibrosis.	[130]
Zebrafish model of chronic infection	Intraperitoneal injection of bacterial strain in adult wildtype and mutant zebrafish	Study the effect of various *M. abscessus* R and S strain infection and differences in immunopathogenesis.	Development of heterogenous mix of free bacteria around the peritoneal cavity. Necrotic granuloma formation was reduced in both tnfr1 and tnfr knockdown animals infected with R strain while its was unaffected in S strain.	[131]
Zebrafish model of cystic fibrosis	Morpholino injection in zebrafish embryo developed for cftr and myd88 loss-of-function	To investigate the immunomodulatory action of four-phage cocktail in cftr loss-of-function zebrafish model	Phages alleviate inflammation in zebrafish by supressing pro-inflammatory cytokine expression and reducing neutrophilic recruitment in the infection site.	[132]
Zebrafish gill inflammation model	Adult zebrafish gill wounded through cryoinjury	Study the novel model of respiratory tissue damage in gills through cryoinjury	Recruitment of neutrophils and macrophages in the wounded area. Expression of cxcl18b was persistent throughout the time course while IL1β and IL6 expression was observed to be maximum at 9th and 15th hour respectively post-injury.	[133]
Zebrafish model of gill inflammation	Adult zebrafish wounded through gill resection	Study the ability of zebrafish to regenerate gill filaments and replace respiratory chemoreceptors	After 24 h of resection, within 24 h of resection, a new mass of proliferating cell nuclear antigen positive cells appeared at the filament tip. Approximately half of the resected tissue was replaced post 40 days post-resection.	[134]
Zebrafish model of gill inflammation	Development of mutant zebrafish line through CRISPR/Cas9	Study the effects of IL-4/13A and IL-4/13B in suppressing inflammation and role of IL-10 in mucosal tissue	IL-4/13A are required for the maintenance of a Th2-like phenotype in the gills and mitigation of type 1 immune response. IL-10 is essential for gill homeostasis.	[135]
Zebrafish model of respiratory inflammation	R848 administration in zebrafish	Investigation of mechanistic immune pathways for assessing effects of drug	Early response for TNF-α was observed whereas IFN-γ levels increased consecutively.	[136]
Zebrafish model of respiratory toxicity	Adult zebrafish exposed to polyhexamethylene guanidine phosphate	To evaluate pulmonary toxicity of household chemicals	Increase in mRNA levels of inflammatory factors for 28 days. Infiltration of inflammatory cells and destruction of gill lamellae was observed.	[137]

(*continued on next page*)

Table 2 (*continued*)

Disease Model	Zebrafish stage and infecting agent	Objective of the model	Prominent results	References
Zebrafish model of gill toxicity	Exposure of various microparticles sizes to adult zebrafish	Evaluation of gill disturbance and innate inflammatory reaction.	Upregulation of ifnγ gene in zebrafish gills exposed to 1 and 90 μm beads. The genes il1β and igm in zebrafish gills were also upregulated post exposure.	[138]
Zebrafish model of mucosal inflammation	Cigarette smoke extract exposure to adult zebrafish	To study the molecular mechanisms underlying immunity within a respiratory epithelium	Exposure resulted in an increase in transcripts of proinflammatory cytokines in the gill tissue. Long term exposure of 6 week revealed lamellar fusion and mucus cell formation while signs of inflammation and fibrosis were absent.	[125]
Zebrafish model of neutrophilic inflammation	Zebrafish larvae inflated with swim bladders microinjected with inducers	Studies of alveolar injuries through swim bladder for drug screening	Increased neutrophil recruitment into the swim bladder through blood capillaries around the pneumatic duct. Reduction in neutrophil migration in response to Shp2 inhibition.	[139]
Zebrafish model for Ras-associated inflammation	Development of mutant zebrafish line	Investigate the role of KRAS in zebrafish gills upon inflammation	Targeted expression of EGFP-KRASG12V in zebrafish gills resulted in hyperplasia, activation of the ERK-MAP kinase pathway, and regional inflammation.	[140]

in this meningitis [109]. The induction of meningitis is initiated by pathogen assisted molecular patterns which are detected by receptors and induce cerebral edema and thrombosis (Fig. 2). *In vivo* model of zebrafish is utilized to observe the invasion of *M. marinumin*, within the microglia of the brain, thereby leading to an increase in the expression of proinflammatory cytokines, namely TNF-α, IL-6 and IL-1β [110]. Some of the recent studies on zebrafish model development for bacterial meningitis are illustrated in Table 1.

3.2. Pulmonary inflammation zebrafish model

A transgenic line of folate-deficient zebrafish missing a completely evolved swim-bladder has been used to mimic the pathophysiology of lung injury and study the same [121]. The imbalance between proteases and antiproteases is another important reason for pulmonary inflammation. The partially evolved swim bladder is a result of an imbalance of cathepsin L/zebrafish cystatin B protease/antiprotease caused by the folate deficiency. 5-formyltetrahydrofolate has blocked the swim bladder malformation and the protease/antiprotease imbalance, thereby aiding in the understanding of lung injury during COPD [121]. Recently, a novel model of silicosis was developed in a zebrafish embryo by injection of silica crystals into the hindbrain ventricle to study the molecular activation of the immune system [122]. Similarly, Alqasmi [123], induced a pulmonary inflammation model in zebrafish through cigarette smoke extract which revealed increased cytokine expression and reactive oxygen species in the induced groups. In another zebrafish model, neutrophil accumulation removal in the inflammation sites of the lungs is achieved by C-X-C Motif Chemokine Ligand 12/C-X-C chemokine receptor type 4 signaling in which they concluded that the blocking of the CXCR4 signal enhances the reverse migration of neutrophils [124]. The inflammation in zebrafish gills is being studied as a novel model to understand the formation of mucus cells in the epithelium of the lungs due to cigarette smoke [125]. Similarly, a zebrafish *Candida albicans* infected swim bladder model is used to investigate the role of various respiratory pathogens in lung inflammation. The activation of NF-κB in epithelial cells during high levels of infection as well as its inhibition during low levels of infection are demonstrated [126]. The pulmonary inflammation is primarily associated with neutrophilic infiltration which releases cytokines and protein kinases causing tissue degeneration and fibrosis (Fig. 2) These models can be helpful in investigating the molecular aspects of the onset of the disease. Furthermore, the recent advances in the development and use of these models for therapeutic screening are disclosed in Table 2.

3.3. Atherosclerosis zebrafish model

Due to its optical transparency and physiological similarities to humans in terms of lipid metabolism, zebrafish has become a valuable model for studying atherosclerosis. The most commonly developed model for the study is diet-induced atherosclerosis. Dietary alterations can lead to the deposition of lipids in the vasculature which is a major incident during the onset of atherosclerosis. A hyperlipidemic zebrafish model developed by feeding high cholesterol diet was used to investigate the role of emodin, a natural anthraquinone which reduced hyperlipidemia and inhibited cholesterol synthesis [141]. The knowledge on atherosclerosis pathogenesis in the zebrafish model is gained by utilizing a high cholesterol diet to induce the buildup of lipid by macrophages, which causes the accumulation of foam cells [103]. A model of hypercholesterolemic zebrafish larvae was used to study the early stages of atherosclerosis. It was found that PPAR-γ levels dropped and proinflammatory cytokines like TNF-α and IL-1β levels rose. Moreover, during the early atherosclerosis stage, the accumulation of neutrophils is observed first, followed by the deposition of lipids [142]. One more high cholesterol diet zebrafish model is investigated to establish the role of ezetimibe in decreasing lesions during the early atherosclerosis stage by increasing the expression of apolipoprotein (APO) A-II. Apo A-II has the ability to reverse the transportation of cholesterol and the expulsion of excess cholesterol [143]. High iron levels aid in the development of a hyperlipidaemic zebrafish

model. Abatement of female sterility, increased liver toxicity, and hyperglycemia were observed in the high iron-supplemented zebrafish model. The risk of atherosclerosis is proven to be increased due to fructose and iron-rich food consumption [144]. The lipid metabolism process of zebrafish is similar to that of humans and hence the study can help researchers understand how diet and genetics influence lipid accumulation and plaque formation [145]. Similarly, due to the optical transparency in the zebrafish larvae, they can be subjected to imaging in order to investigate the vascular development and blood flow, which are crucial parameters for atherosclerosis development [146]. As shown in Fig. 3, inducers of atherosclerosis and hypercholesterolemia are high cholesterol diets and chemical inducers that activate specific pathways for the activation of macrophage-derived foam cells and monocyte migration. These pathophysiological factors often collaborate with inflammation, and hence, further investigations can help in understanding the mechanism of atherosclerosis associated inflammation. Further, zebrafish models are used to study the mechanistic insights into the disease prognosis and screening of therapeutic targets as enlisted in Table 3.

3.4. Zebrafish models of intestinal inflammation

Adult zebrafish embryos, larvae, and transgenic zebrafish are being used for the study of IBD. Researchers primarily develop the model through genetic manipulation or chemically-induced inflammation. The most commonly used chemicals to induce inflammation in zebrafish are TNBS and LPS [156–158]. Chemical inducers activate the inflammatory pathways as well as release of heptanated colonic protein, which leads to the activation of Th1 cells (Fig. 3) TNBS- induced colitis models have been developed to observe the structural changes in the plexuse and enteric ganglia, and it is found that there is an increase in the serotonergic neuron proportion in the complete zebrafish intestine [159]. Furthermore, the understanding of intestinal injury to study epithelial barrier function and the effect of PGE2 administration leading to improved epithelial barrier function are also studied [160]. Deficiency of PIK3C3 in a zebrafish model leads to injury in the intestine and infiltration of neutrophils into the epithelium of the intestine as well as an increase in proinflammatory cytokine levels [161]. In a transgenic zebrafish model, immune cell migration, production of various proinflammatory cytokines, and NF-κB pathway activation are blocked by Rhein, a Chinese herbal component [162]. Researchers investigate the variation in the microbiome due to interhost dispersal in both wild-type and myd88 knock-out zebrafish [163]. Glafenine is used as an inducer of injury in the zebrafish intestine, and μ-opioid receptor signalling inhibition by μ-opioid agonist DALDA is done to reduce the injury [164]. Retinoic acid reduces the production of intestinal mucin in a DSS-induced colitis model [165]. Another zebrafish model is utilized for studying the function of intestinal alkaline phosphatase in detoxifying LPS and thereby, inhibiting the inflammation of the intestine in acknowledgment of the resident microbiota [166]. Zebrafish models are also used to study the integrity of the gut barrier and its prognosis during IBD. Furthermore, various bacterial strains have been used to investigate the role of the gut microbiome in IBD development [167,168]. Various drugs have been studied and are currently being investigated through the zebrafish model to reveal their inflammation suppressing effects, investigate the role of gut the microbiome, and disease mechanisms, as mentioned in Table 4.

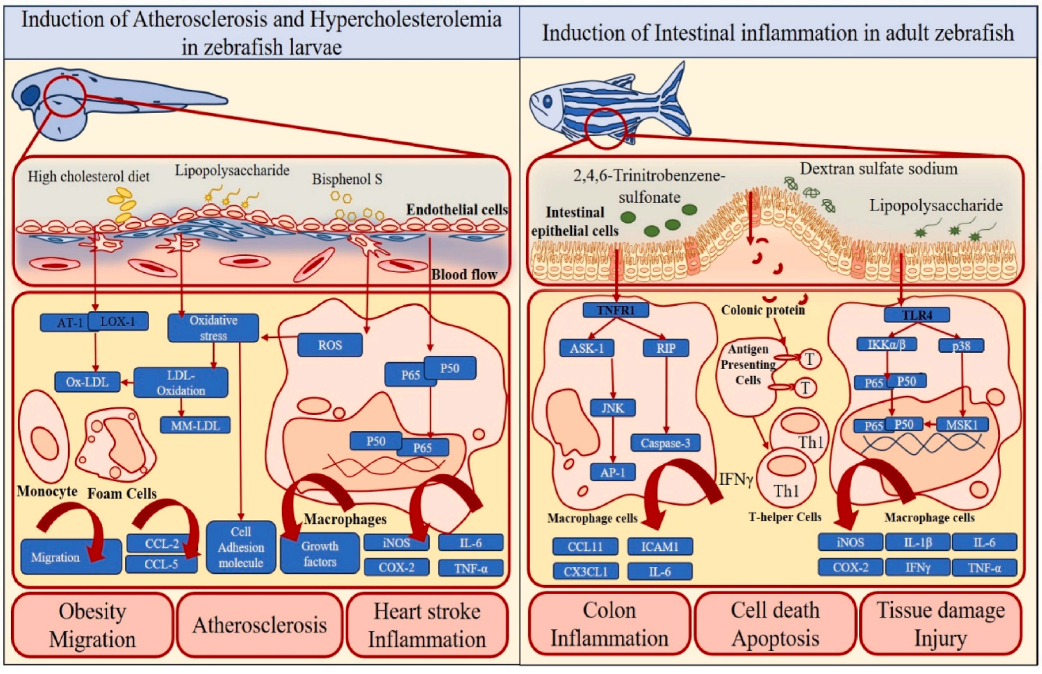

Fig. 3. Diagrammatic representation of molecular induction of Atherosclerosis, hypercholesterolemia, and intestinal inflammation in zebrafish model.

Table 3
Recent studies on zebrafish models for coronary inflammation and atherosclerosis.

Disease Model	Zebrafish stage and infecting agent	Objective of the model	Prominent results	References
Zebrafish model of Atherosclerosis	Zebrafish larvae fed with high cholesterol diet	Investigate the role of bioactive peptide HPAEDR	Peptide treatment revealed reduced oxidative stress, anti-inflammatory effects and inhibits the formation of atherosclerotic plaque.	[141]
Zebrafish model of atherosclerotic cardiovascular disease	Zebrafish larvae exposed to Bisphenol S	Develop a model accelerating the progression of atherosclerotic cardiovascular disease	Recruitment of macrophages around blood vessels, accumulation of oxidized low-density lipoproteins on vascular endothelium. Lipid accumulation in caudal artery and thickening due to collagen fibres.	[147]
Zebrafish model of Atherosclerosis	Stabilin 1/2 knockout zebrafish larvae fed with high cholesterol diet	Investigate the role of stabilin 1/2 in oxidized low-density lipoprotein clearance	Deficiency of stab 1 and stab 2 strongly upregulated the clearance of lipoproteins by macrophages within the caudal vein.	[148]
Zebrafish model of lipid metabolism disorder	ApoEb knockout zebrafish using CRISPR-Cas9	Establish a model for lipid metabolism disorder to study hypercholesterolemia	ApoEb mutant showed significantly increased lipid levels. Simvastin, ezetimibe and Xuezhikang reduced the recruitment of neutrophils and macrophages.	[149]
Zebrafish model of Atherosclerosis	Zebrafish larvae fed with high cholesterol diet and lipopolysaccharide	Develop efficient model of atherosclerosis for high-throughput screening of drugs	Formation of plaques in the zebrafish blood vessels containing fibrous tissue and lipids. Increased severity when induced with both high cholesterol diet and lipopolysaccharide compared to individual treatment.	[150]
Zebrafish model of Atherosclerosis	Zebrafish fed with high cholesterol diet	Investigate the protective activity of *Dendrobium huoshanense* Polysaccharide	Treatment of polysaccharide decreased plaque formation, neutrophil recruitment, and levels of total cholesterol in high cholesterol diet induced larvae.	[151]
Zebrafish model of cardiovascular disease	HEG1 knockout zebrafish using CRISPR-Cas9	Study the mechanism and pathophysiology of cardiovascular diseases.	Mutant embryos exhibited atrial ventricular enlargement, heart rate slowing, and reduced blood flow rate. Further pericardial swelling and Edema was also observed.	[152]
Zebrafish model of ischemic stroke	Zebrafish larvae exposed to Ponatinib	Study cellular and molecular pathogenesis of ischemic stroke and screen therapeutics	Induction with Ponatinib reduced motility, blood flow, presence of inflammation, apoptosis and cerebral vascular endothelial injury.	[153]
Zebrafish model of dyslipidaemia and atherosclerosis	Zebrafish larvae fed with high cholesterol diet	Study the disease etiology and high-throughput screening of the novel targets.	Overfeeding and cholesterol supplementation had pro-atherogenic effects. Causative agents for circulating lipids and early-stage atherosclerosis were revealed to be LPAr2 and GATAD2A.	[154]
Zebrafish model of Atherosclerosis	Zebrafish larvae fed with high cholesterol diet	Investigate the role of ezetimibe and apolipoprotein A-II in reduction of atherosclerosis	High cholesterol diet induction resulted in macrophage recruitment and vascular lipid accumulation. Ezetimibe increased expression of Apo A-II through HNF4 and PPARα transcriptional factors	[143]
Zebrafish model of atherosclerosis	Zebrafish larvae fed with high cholesterol diet	Investigate the role of indole-3-carbinol in treating hyperlipidaemia	Increased lipid accumulation on blood vessel wall in induced larvae which was reduced through Indole-3-carbinol treatment. The mechanism responsible was increased autophagy through the class III PI3K/Akt/mTOR pathway	[155]
Zebrafish model of hypercholesterolemia	Zebrafish larvae fed with high cholesterol diet	Explore the early effects of atherogenesis	Induced endothelial inflammation was observed to be an earlier alteration than neutrophil accumulation. Endothelial inflammation was a result of PPARγ downregulation and elevated TNFα and IL-1β.	[142]

4. Challenges and future prospectives

Although, zebrafish are a versatile model organism for research in inflammation and other biological investigations, they have a lot of challenges that need to be addressed in order to improve the model outcomes. One of the most common limitations of the zebrafish model is their differences in anatomy, physiology, and immune response as compared to higher order mammalian models and humans. Furthermore, the quality of water, temperature, can significantly impact zebrafish health and ultimately change the experimental outcomes making the studies less reproducible. The short gestation time and rapid development is an advantage for zebrafish researchers, as the progression of diseases, inflammation, and the effects of therapeutics can be studied in a short period of time [178, 179]. Although, due to quick development, zebrafish exhibit genetic variability which makes the uniformity of the experimental population challenging. Another major limitation of the zebrafish model is the functional redundancy, where the compensatory mechanisms mask the effects of genetic manipulations, which leads to difficulty in investigating gene functions. To study

Table 4
Recent investigations on zebrafish models for intestinal inflammation.

Disease Model	Zebrafish stage and infecting agent	Objective of the model	Prominent results	References
Zebrafish model of IBD disease	trmt5 knockout zebrafish using CRISPR-Cas9	Study the mechanisms of pathogenic genes	Zebrafish late larval stage was observed with intestinal defects. Inflammatory response was activated along with the increase in intestinal defects.	[169]
Zebrafish model of IBD disease	0.5 % dextran sulfate sodium exposed to zebrafish larvae	Investigate the role of chrysanthemum stem and leaf extract in alleviating inflammation	Induction leads to increased secretion of acidic mucin in the intestine, and the emergence of intestinal inflammation. Flavonoids and phenolic acids from the extract can improve intestinal inflammation.	[170]
Zebrafish model of IBD disease	Adult zebrafish injected intraperitoneally with bacterial lipopolysaccharide	Study the anti-inflammatory effects of drug loaded nanocarrier system	Chronic inflammation in the gill lamina, as well as intestinal tissue of lipopolysaccharide injected zebrafish group.	[10]
Zebrafish model of intestinal inflammation	Zebrafish larvae exposed to 2,4,6-trinitrobenzenesulfonate	Study the intestinal inflammation in different wild type zebrafish	AB type developed higher neutrophilic intestinal infiltration, reduced number of goblet cells and reduced cytokine levels compared to Tübingen type.	[157]
Zebrafish model of colitis	Zebrafish larvae exposed to 2,4,6-trinitrobenzenesulfonate	Investigate the role of short chain fatty acids in suppressing inflammation	Short chain fatty acids increased the survival of induced larvae. Induction led to increase in neutrophil recruitment and expression of inflammatory cytokines which was reduced by short chain fatty acids.	[171]
Zebrafish model of intestinal inflammation	Adult zebrafish injected intraperitoneally with bacterial lipopolysaccharide	Study the anti-inflammatory effects of marine derived bioactive peptide	mRNA levels showed increased expression of inflammation related genes upon induction which was found to be downregulated post peptide treatment.	[101]
Zebrafish model of IBD disease	Zebrafish larvae exposed to 2,4,6-trinitrobenzenesulfonate	Study the anti-inflammatory effects of traditional Chinese medicines	Induction caused increased intestinal neutrophil accumulation, elevated reactive oxygen species levels. Compound inhibited elevated inflammatory factors such as IL-1β, CLCX8a, MMP and TNF-α	[172]
Zebrafish model of IBD disease	ttc7a knockout zebrafish using CRISPR-Cas9	Investigate the role of leflunomide in supressing intestinal inflammation	The histopathological sections revealed crowding o intestinal epithelial cells, breaches in intestinal mucosal layer, and atresia along the intestinal tract which was improved by leflunomide treatment.	[173]
Zebrafish model of intestinal inflammation	Zebrafish larvae fed with soybean meal-based diet	Study the intestinal integrity and function upon soybean meal induction	Increased epithelial permeability, changes in mRNA levels of tight junction proteins. Increased neutrophil replacement and decrease in the microbiota composition.	[174]
Zebrafish model of intestinal inflammation	rag-1 deficient zebrafish larvae fed with soybean meal-based diet	Study the intestinal integrity and function upon soybean meal induction	Macrophages underwent morphological changes. Soybean meal diet induced Th17 response. The induction is T-cell dependent.	[175]
Zebrafish model of enterocolitis	Adult zebrafish injected rectally with 2,4,6-trinitrobenzenesulfonate	Investigate relation between neuro-immune interaction and gastrointestinal motility	Inflammatory reaction reached peak at 6-h post injection and returned to baseline after 3 days. Proportion of cholinergic neuron was significantly reduced in the distal intestine.	[159]
Zebrafish model of colitis	Zebrafish larvae exposed to 2,4,6-trinitrobenzenesulfonate	Study the effects of probiotics during intestinal inflammation	*L. rhamnosus* HN001 strain reduced inflammatory factor IL-6 and restored TGFB-1 while *B. animalis* subsp. lactis Bi-07 was associated only with TGFb-1 elevation.	[168]
Zebrafish model of intestinal injury	Dextran sulfate sodium exposed to zebrafish larvae	Investigate the model to test novel therapeutics that target epithelial barrier	Prostaglandin E2 administration protects against mucosal injury by enhancing epithelial barrier function	[160]
Zebrafish model of inflammatory lymphangiogenesis	Zebrafish larvae exposed to 2,4,6-trinitrobenzenesulfonate	Investigate the role and mechanism of lymphangiogenesis in inflammatory diseases	Induction resulted in vascular endothelial growth factor receptor dependent lymphangiogenesis in the zebrafish intestine. 5-aminosalicylic acid reduced the inflammation and lymphatic expansion.	[176]
Zebrafish model of IBD disease	Zebrafish larvae exposed to 2,4,6-trinitrobenzenesulfonate	Model development for medium-throughput compound screening.	Upon induction, the gut of larvae was dilated, reduction in villus length, expansion of crypts and formation of ileus was observed.	[177]

inflammation, a detailed investigation on immune responses is important. To overcome these challenges, accelerate the drug discovery and development processes, researchers around the globe are working on limiting these downfalls and developing target specific models for inflammation. CRISPR/Cas9 technology is widely integrated in zebrafish studies which can enable the researchers to generate zebrafish lines with precise gene mutations related to inflammation [180–182]. Moreover, for IBD, various studies are being performed to learn about the interaction between the zebrafish gut microbiome and the immune system [178,183,184]. Various *in vivo*

imaging studies can enable real-time visualization of the progress of inflammation and the effects of drugs in suppressing the same. Furthermore, the integration of transcriptomics and proteomics data can deepen the understanding of immune responses in zebrafish. Furthermore, the zebrafish model can be studied to identify rare cell types and their functions during inflammation by applying a single-cell RNA sequence to zebrafish models [185,186]. Overcoming these, the time frame for the development of novel anti-inflammatory therapeutics can be reduced, and the preclinical phase can be accelerated.

5. Conclusions

Chronic inflammation is a significant issue affecting patients with IBD, bacterial meningitis, COPD, and atherosclerosis. Various anti-inflammatory drugs are prescribed to manage symptoms, but the development of novel therapeutics for curing inflammation is increased radically due to several adverse effects revealed by the existing drugs. Zebrafish models, which have been developed through chemical induction, wounding, and mutations, are commonly used to confirm the efficacy of these drugs. Zebrafish models provide a detailed insight into the cellular and molecular aspects of therapeutics and their toxicological effects. Researchers can explore conserved mechanisms and potential therapeutic targets of novel drugs through zebrafish models. However, it is crucial to validate the results obtained in zebrafish models in more complex mammalian models before considering these therapeutic approaches for human use.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Akshad Balde: Writing – original draft, Validation, Data curation. **Cunnathur Saravanan Ramya:** Writing – original draft, Formal analysis. **Rasool Abdul Nazeer:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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