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Blue Light Effects on Zebrafish: A Comprehensive Review

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Abstract: Blue light exposure in zebrafish affects oxidative stress, neuronal activity, behavior, development, and circadian rhythms. While moderate exposure can enhance visual function and neuroprotection by regulating antioxidant genes, prolonged exposure may lead to harmful effects. To identify relevant studies, specific literature searches were conducted across Scopus, Web of Science, and ScienceDirect. Duplicate and irrelevant publications were eliminated. Findings indicated that blue light has notable positive effects, including enhancing antioxidant gene expression to decrease oxidative stress, promoting neurogenic plasticity, improving circadian rhythms, and supporting development. However, it also presents significant risks. Prolonged or high-intensity blue light exposure can induce oxidative stress, overwhelm cellular defense mechanisms, and lead to potential damage. This review explores the effects of blue light exposure in zebrafish, covering molecular changes, behavioral responses, and physiological impacts to provide a comprehensive understanding of its influence.

Keywords: blue light; zebrafish; danio rerio.

1. Introduction

Danio rerio, also known as zebrafish, has become a popular model in biological research because of its rapid growth and genetic resemblance to humans [1]. Zebrafish are valuable model organisms for biological and biomedical research due to their ease of availability, readily accessible embryos, high embryo yield, and lower space requirements for setting up zebrafish husbandryClick or tap here to enter text.,3]. Every week, female fish lay a lot of eggs, and the embryos go through six phases of rapid outward development: 0-72 hours post-fertilization, hpf (pre-hatching embryos), 72-120 hpf (post-hatching), 5-29 days post-fertilization, dpf (larval), 30-89 dpf (juvenile), 90 dpf – 2 years (adult), and from 2 years (aged) [4]. Zebrafish embryos are also used because of their transparency, which enables visualization oforphological disorders, functional genetics, and gene characterization [5]. In terms of gene resemblance, the zebrafish genome shows similarities to humans in protein-coding genes and the number of chromosomes

(25 pairs in zebrafish and 23 pairs in humans [6]. Compared to other animals, zebrafish offer several advantages, such as low cost, high breeding rates, and HTS (Table 1). According to the fully sequenced zebrafish genome, 84% of genes associated with human disease have a zebrafish homologand 70% of human protein-coding genes are linked to zebrafish genes [10].

Table 1. Animal model comparison [7,8,9].

Animal / Aspect	Rat	Rabbit	Monkey	Pig	Cat	Dog	Zebrafish
Cost	Moderate	Moderate	High	High	Moderate	Moderate	Very Low
Breeding Rate	Moderate	Moderate	Low	Low	Low	Low	Very Hight
High-throughput screening (HTS)	Moderate	Moderate	Low	Low	Low	Low	Very High
Anatomical similarity to humans	Moderate	Good	High	High	Moderate	Moderate	Low
Genetic similarity to humans	86.5%	88%	96.8%	89.4%	90%	84%	84%

Since the zebrafish genome was recently sequenced, there are several chances to compare it to the genomes of other animals. The human eye is sensitive to the visible spectrum of light, which ranges from violet light with a wavelength of approximately 380 nanometers (nm) to red light with a wavelength of about 780nm [11]. The colors of violet, indigo, blue, green, yellow, orange, and red are associated with this region (380nm-780nm) of the electromagnetic spectrum [12]. The visible spectrum's highest energy band is blue light, which ranges from 380 to 500 nm and is primarily classified as either blue-violet (405nm-455nm) or blue-turquoise (460nm to 500nm) [13]. Both artificial and natural light sources emit blue light [14]. Although natural sunlight continues to be the dominant source of blue light, accounting for around 25% of emissions, artificial sources, including fluorescent lights, LED screens, and digital devices, also produce significant amounts of blue light [15].

Blue light has increasingly been recognized for its detrimental effects on retinal health. Compared to longer wavelengths such as red or green light, blue light is more deeply absorbed by the eye and has been demonstrated to induce significant phototoxicity, particularly in retinal pigment epithelium (RPE) cells [16]. Oxidative stress mechanisms primarily drive light-induced damage, as exposure to blue light promotes the production of reactive oxygen species (ROS). This phenomenon leads to mitochondrial dysfunction, lipid peroxidation, and cellular apoptosis [17, 18]. Lipofuscin is important in this process; it is a pigment that glows under certain light and builds up in RPE cells as people get older. When it is exposed to blue light, it can cause more damage to the cells. These pathological processes are closely associated with the onset and progression of age-related macular degeneration (AMD), a leading cause of irreversible vision loss in the elderly [19]. Display technology has evolved over the years, transitioning to smaller and more portable devices. Current and future display advancements enable digital miniaturization, bringing displays from an arm’s length closer to the eye [20]. The time spent on an electronic screen is almost 3 times that of a conventional printed task, and this is also associated with visual and musculoskeletal symptoms [21]. One characteristic of contemporary digital life is the widespread use of blue-light-emitting devices, particularly among college students, a demographic known for significantly higher daily screen time. Yeşilırmak *et al*. [22] found that students reported an average of 8.88 hours of screen time each day, which consisted of using a computer (3.18 hours), smartphone (5.2 hours), and television (0.5 hours). 93.8% of participants identified televisions,

laptops, and phones as the primary sources of blue light, underscoring the prevalence and recognition of these devices in everyday life. With the increasing reliance on digital devices and LED-based lighting, prolonged exposure to blue light has become a significant and pressing environmental risk factor for retinal degeneration. This situation has raised concerns about the long-term effects of extended blue light exposure, particularly from digital devices, which have become essential in modern life [23]. Although blue light can harm and strain the eyes, it is also essential for controlling circadian rhythms [24]. Circadian rhythms function as biological clocks in the brain, carefully regulating activities related to morning and nighttime within a 24-hour cycle [25]. This cycle is affected by non-visual photoreception and involves the detection of light through pathways apart from the rods and cones [26]. However, excessive exposure to blue light can disrupt melatonin production, making it difficult for individuals to sleep and maintain quality rest [27]. This disruption has been associated with numerous health problems, including sleep disorders, mood disturbances, developmental issues, and even chronic conditions.

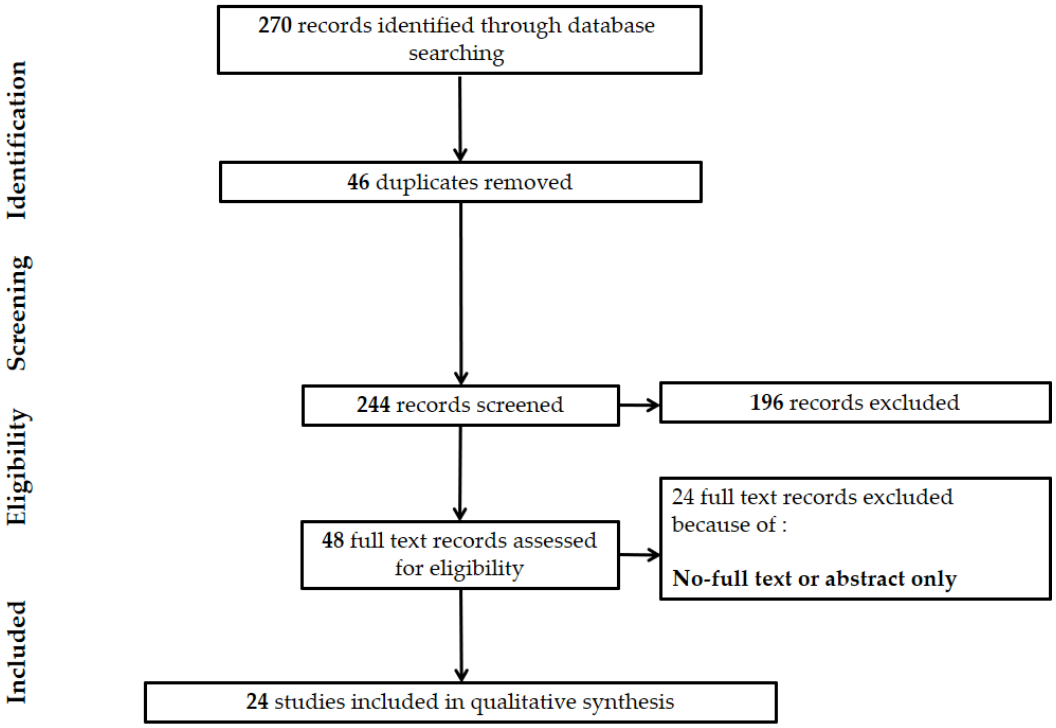

Figure 1. PRISMA Flow Diagram.

Given these concerns, zebrafish have emerged as a valuable in vivo model for studying light-induced retinal damage. Zebrafish possess a cone-rich retina that closely resembles the human macula, enabling relevant investigation of photoreceptor and RPE cell pathology [28]. Optical transparency during early development enables noninvasive imaging of retinal structures, ROS accumulation, and mitochondrial changes in response to blue light [16]. Furthermore, their rapid development, genetic tractability, and high reproductive capacity support high-throughput experiments and thorough molecular analyses [29]. These features make zebrafish particularly suitable for investigating how blue light can damage the retina at both cellular and molecular levels, as well as for exploring potential protective measures against such damage. Consequently, using blue light as an inducer and zebrafish as a model organism provides a strong, relevant platform to enhance our understanding of retinal degeneration and facilitate the development of innovative therapeutic strategies.

This review will investigate the effects of blue light on various molecular, physiological, and behavioral aspects of zebrafish. It focuses on the dual impacts of blue light exposure,

highlighting its influences on oxidative stress, neurobehavioral outcomes, circadian rhythms, and physiological development.

2. Materials and Methods

This narrative was initiated by employing targeted keywords, such as "Blue light and Zebrafish, "Blue light and Danio rerio," and “Light exposure and Zebrafish”, to locate pertinent literature. The search was performed on Scopus, excluding irrelevant articles. Subsequently, the Web of Science (WOS) database was queried, duplicates previously discovered in Scopus were eliminated, and unrelated research was excluded. A comparable procedure was conducted on ScienceDirect to guarantee thorough coverage. Upon completion of these stages, the residual articles were categorized according to their thematic focus. Each category was thereafter examined independently, with the findings meticulously analyzed and synthesized to compose the review (Figure 1).

3. Results

3.1. Blue light effects on zebrafish oxidative stress.

Multiple studies have shown that blue light exposure has both beneficial and detrimental effects on zebrafish, depending on the characteristics of exposure, including wavelength, intensity, and duration. Blue light significantly impacts zebrafish health by inducing oxidative stress, apoptosis, retinal damage, and visual dysfunction. All findings in Table 2 have been thoroughly summarized and visually depicted in Figure 2. This image provides a comprehensive summary, illustrating the principal results from each study and emphasizing the impact of various blue light exposure settings on zebrafish.

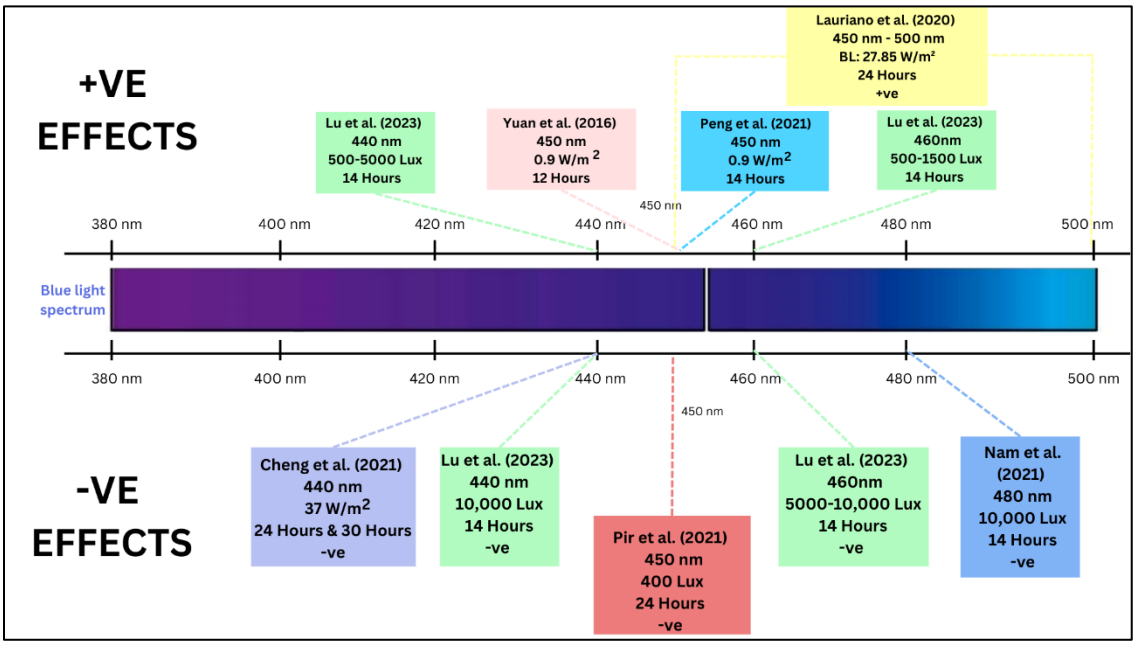

Figure 2. Summary of findings: blue light effects on oxidative stress of zebrafish.

Table 2. Blue light effects on zebrafish oxidative stress.

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
[30]	Blue LEDs: peak 450nm	0.9 W/m²	5 weeks	BL: • Reduced oxidative damage (liver) • Reduced ROS production RL:	Age of Zebrafish: Female zebrafish (AB strain) about 5 weeks of age

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
	Red LED: peak 630 nm A white fluorescent bulb			• Increased oxidative stress in the liver • Increased lipid peroxidation WFB: • No induces oxidative stress	
[31]	Blue LEDs: 450 nm White LEDs (Control)	0.9 W/m²	2 weeks	BL: • Reduced the adverse effects of cold on zebrafish • Improved antioxidant and phototransduction-related markers WL: No inflammatory response seen	Age of Zebrafish: 3 months old (AB strain) Cold exposure caused oxidative stress
[32]	Blue LEDs: peak 450 nm White LED: Control	0.9 W/m²	2 weeks	BL: • Reduced lipid peroxidation and apoptosis • Reduced oxidative stress • Mitigated cold shock effects on zebrafish WL: • No inflammatory response • Increased oxidative stress	Age of Zebrafish: 3 months old (AB strain)
[33]	Blue light: 440 nm and 460 nm Red light: 650 nm	500, 1,000, 1,500, 5,000, and 10,000 lux	4 days	BL 440 nm: • 500 lux: Slight improvement on optokinetic response (OKR) (6h), mild OKR enhancement (14h), and no retinal thinning. • 1000 lux: Moderate improvement on OKR(6h) and mild thinning in OKR (14h) • 5000 lux: Significantly enhanced on OKR (6h), maximal OKR enhancement (14h), and an early sign of ONL thinning. • 10,000 lux: OKR peak (6h) and OKR slight decline (10h). Only thinning occurred (14h). BL 460 nm: • 500 lux – 1000 lux: OKR improved (6h), OKR peak (10h). OKR declined showed minimal retinal effects (14h). • 5000 lux: Slight improvements in OKR (6h) and OKR declined (10h). Minimal retinal damage (14h). • 10,000 lux: OKR peak (6h-10h) but no significant retinal thinning (14h) RL: • 500 lux: Slight OKR improvement (6h) and OKR maintained (10h-14h) • 1000 lux: Slight OKR improvement (6h) and OKR declined (10h). Mild ONL thinning (14h). • -5000 lux: Moderate OKR enhancement (6h), early ONL thinning (10h), and increased at (14h). • 10,000 lux: ONL thinning pronounced (6h). Retinal damaged	Age of Zebrafish: From 3 dpf to 6 dpf. The effect worsened as the duration increased
[34]	Blue LEDs: 500 nm White-blue light: 400 nm–500 nm	BL: 27.85 W/m² WL: 93.46 W/m²	10 days	BL: • Increased Calbindin-D28K and calretinin • Decreased oxidative stress WL: • Less pronounced Calbindin-D28K and calretinin • A decrease in oxidative stress	Age of zebrafish: 3 months old
[35]	Blue light LEDs: 480nm	10,000 lux	4 Days	• Retina damage • increased levels of ROS • Activated pro-apoptotic pathways	Age of Zebrafish: 6 months post-spawning.

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
[16]	Blue LEDs: 440 nm	37 W/m²	2 Days	24Hours: • Decreased the thickness of the retinal layer • Activation of apoptosis 30 Hours: • Further thinning of retinal layers • Increase apoptosis signaling	Age of Zebrafish: 4 dpf
[36]	Blue: 450 nm Green: 530 nm Red: 630 nm White: Broad-spectrum fluorescent bulb	400 lux	5 days	BL: • 28°C: Minimal oxidative stress • 29°C: Slightly increased oxidative stress • 30°C: Moderate increase in development and stress marker GL: • 28°C: Moderate oxidative stress and minor lipid accumulation • 29°C: Increased stress marker, mild developmental changes • 30°C: Noticeable oxidative stress and apoptosis RL: • 28°C: High oxidative stress, apoptosis, and lipid accumulation • 29°C: Increased mortality • 30°C: High in mortality rates and oxidative stress. Severe malformations WL: • 28°C: High mortality • 29°C: Significantly increased oxidative stress, apoptosis, and lipid accumulation • 30°C: Highest mortality rates and oxidative stress, developmental damage	**Age of Zebrafish**: from 4hpf to 120 hpf. The experiment involved three temperature groups set at 28°C, 29°C, and 30°C

Blue light, in contrast, prevented oxidative damage, primarily because of its limited penetration into water, which reduces ROS formation. The research conducted by Yuan *et al*. [30] showed that exposure to blue light with a peak wavelength of 450 nm at an intensity of 0.9 W/m² for 12 hours over a five-week period did not negatively affect fish growth. Instead, it exhibited a protective impact on the liver. This impact was associated with steady hepatic energy reserves, with no significant alterations in the hepatic somatic index (HSI) and an increased antioxidative response, as evidenced by elevated activity levels of the Copper/Zinc Superoxide Dismutase (Cu/Zn-SOD) and Catalase (CAT) enzymes. Moreover, exposing subjects to blue light at the same intensity for 14 hours over a 2-week period eviated the adverse effects of cold stress, enhancing survival rates, maintaining retinal structure, and modulating antioxidant and apoptotic responses, thereby reducing cold-induced damage to retinal tissue and gene expression [31,32]. Lu *et al*. [33] conducted a study in which zebrafish were exposed to blue light at 440 nm (500-5000 lux) and 460 nm (500-1500 lux) over four consecutive days, revealing a positive effect at moderate light intensities. The research has shown a beneficial effect on visual function, as evidenced by increased levels of tyrosine hydroxylase and dopamine transporters, driven by enhanced optokinetic responses and increased dopamine production. These effects were observed at moderate exposure levels, suggesting that blue light may be therapeutic when well controlled. Notably, exposure to 440 nm blue light at these intensities did not result in considerable retinal damage, suggesting that lower levels of exposure may be advantageous for visual function. Lauriano *et al*. [34] established that Blue light exposure (400–500 nm) with an irradiance of 27.85 W/m², administered continuously for 24 hours over 10 days, resulted in a notable enhancement in

the production and colocalization of Calbindin-D28K and calretinin within club cells. These proteins were shown to protect against oxidative stress induced by short-wavelength light by activating metabolic pathways that generate photo-protective compounds.

On the other hand, exposure to blue light is associated with severe dangers, particularly when blue light exposure is protracted or intense. Nam *et al*. [35] demonstrated that exposure to blue light (480 nm) at 10,000 lux for 14 hours over 4 days resulted in significant histological damage in the retina, with the photoreceptor layer notably affected. Additionally, it led to an increase in the formation of ROS, which resulted in oxidative stress and cellular damage. In other cases, high intensity caused retinal thinning and a loss in visual function, underscoring the hazards associated with excessive exposure to blue light. Lu et al. [33] demonstrated that when exposed to 10,000 lux of blue light, the beneficial effects decreased, and the zebrafish displayed signs of retinal thinning, suggesting possible retinal damage. This finding indicates a threshold effect, in which high-intensity exposure results in retinal damage despite the initial enhancements in visual function observed at lower intensities. The response at 460 nm suggests a nuanced equilibrium: moderate exposure may confer benefits for visual health, while excessive exposure could lead to negative consequences. Moreover, Cheng *et al*. [16] demonstrated that exposure to blue light (440 nm) for 24 to 30 hours triggered oxidative stress and apoptosis in retinal pigment epithelial cells, leading to DNA damage, as evidenced by γH2AX overexpression, a biomarker of the DNA damage response. Initially, autophagy was engaged as a protective mechanism against cellular damage; however, prolonged exposure disrupted this process, exacerbating oxidative stress and cellular apoptosis. Pir *et al*. [36] investigated the impact of blue light (450 nm) at 400 lux over a duration of 24 hours. They discovered that this exposure resulted in moderate survival rates at lower temperatures (28°C), but it significantly increased mortality rates and oxidative stress at higher temperatures (30°C). The combination of blue light exposure and elevated temperatures exacerbated physiological dysfunction and abnormalities, highlighting the detrimental effects of blue light in stressful environmental conditions.

Significant variations largely account for the contradictory findings regarding the effects of blue light exposure on zebrafish across experimental models, exposure parameters, and environmental contexts. Research on adult zebrafish indicates that exposure to blue light at moderate levels of approximately 0.9 W/m² may provide protective benefits during prolonged exposure. These studies have found that blue light can reduce oxidative damage, boost the activity of antioxidant enzymes, and help maintain retinal structure, especially when the fish are under stress, such as cold water [30]. Conversely, research on embryonic and larval stages indicates significant vulnerability to blue light, particularly at high intensities up to 10,000 lux or brief but intense exposure durations. Lu *et al*. [33] discovered that moderate intensities (500–1500 lux) enhanced visual function and dopamine-related activity, while higher intensities resulted in retinal thinning and a decline in functional health. Similarly, Cheng *et al*. [16] found that larvae showed greater retinal cell death and DNA damage after exposure to blue light at 440 nm for 24–30 hours, highlighting that the developmental stage is an important factor in their vulnerability. These discrepancies illustrate the value of considering the developmental context when interpreting the biological effects of blue light. In addition, the duration of exposure and intensity play a critical role; prolonged exposure, even at moderate intensities, can result in cumulative oxidative damage. This effect is evidenced by increased retinal damage observed following continuous exposure to high-intensity blue light in several studies [16, 35]. Taken together, these factors highlight that the biological effects of blue light are highly context-dependent, influenced by an interplay of developmental stage, light intensity, and exposure time. To clarify these complexities, future studies should use the same experimental setups with controlled factors and conduct direct

comparisons across developmental stages and light conditions to determine safe limits for blue light exposure.

3.2. Blue light effects on the development of zebrafish.

Blue light, with wavelengths between 450 and 480 nm, has been demonstrated to affect zebrafish growth, survival, and physiological development. Under optimal conditions, blue light can promote growth and enhance processes such as visual system maturation and immune responses. However, excessive exposure or high intensity can disrupt the normal development of zebrafish. Figure 3 synthesizes and illustrates the results shown in Table 3. This visual representation offers a concise overview of the key findings, highlighting how different parameters of blue light exposure affect zebrafish development.

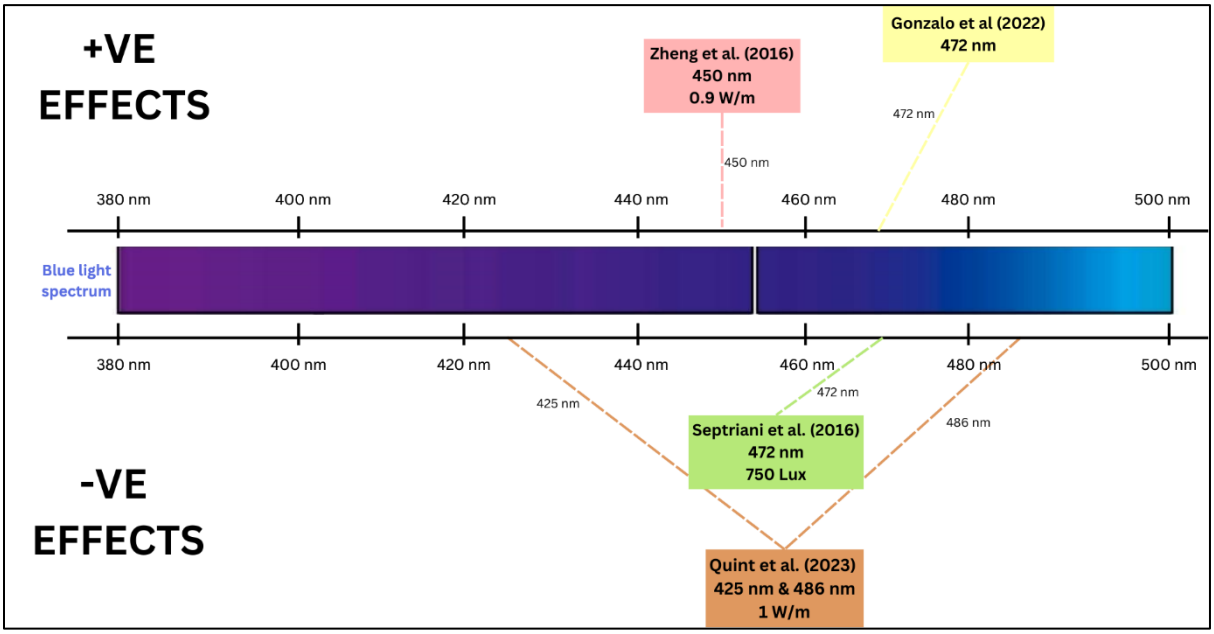

Figure 3. Summary of findings: blue light effects on the development of zebrafish.

Table 3. Blue light effects on development.

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
[37]	White fluorescent bulb Blue LED light: peak 450 nm Red LED light: peak 630 nm	0.9 W/m²	8 weeks	BL: • Increase growth in zebrafish. • Increased serum globulin levels. • Upregulated activities of immune-related enzymes • Positive correlation between immune gene expression and protein levels RL: • Reduced the growth of zebrafish • Reduced globulin level • Decreased activities of immune-related enzymes • Decreased correlation between the immune gene and protein level WL: • Intermediate result.	Age of Zebrafish: 8 weeks
[38]	Blue: peak 472 nm White: peaks at 466 nm and 668 nm Red: peak 665 nm.	N/A	30 days	BL: • High hatching rates and survival • Stimulated growth, food intake, and somatic growth factor gene expression • Reduced stress-related expression level RL: • Lowest hatching rates and survival	Age of Zebrafish: 0 to 30 dpf.

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
				• Larvae died during development • Elevated stress-related expression level WL: Higher hatching rates and survival	
[39]	Violet: 425nm Cyan: 483 nm UVA: 369 nm Green/yellow: 557 nm Red: 633 nm White light: - Broad-spectrum (day) light	UVA: 0.25 W/m² above 400 nm: 1 W/m² WL: 0.03 W/m² daylight:2.78 W/m²	3 continuous months	Cyan Light: Significantly reduced axial length Violet Light: Mild effect with cataracts in 12.5% of fish UVA Light: Severe ocular damage, including cataracts, microphthalmia, and aphakia in 18.8% of fish Green/Yellow Light: No significant effect on axial length Red Light: Reduced axial length compared to both white and dim light controls at 3 mpf. Broad-spectrum Daylight: Supported normal development, preventing UVA-induced damage.	Age of zebrafish: 5dpf until 3 months post-fertilization (mpf).
[40]	Blue Light: 472nm Green Light: 436nm Red Light: 665 nm White Light 668nm	750 lux	10 days	BL: • Lowest survival rate • Increased malformation • Significantly inhibited body length and head height. • Inhibited eye pigmentation and retinal development RL: • Moderate rate of survival • Inhibited growth and the retinal layer • Mild impact on retinal pigmentation • Increased expression of red-sensitive opsin gene GL: • Highest survival rate • Minimal malformation • Favorable impact on eye diameter and retinal pigmentation WL: • High rate of abnormalities • Mild effects on retinal pigmentation	Age of Zebrafish: 1 dpf to 10 dpf
[41]	Fluorescent: Red Light Blue light Green White light LED: Blue light, Green light, red light cool room light(control)	Isolation Box Experiment: Red light: 226 lux Blue light: 366 lux Green light: 624.3 lux White fluorescent light: 2099 lux Room light (control): 228.2 lux iSpawn-S experiment: Red light: 6.5 lux Blue light: 2.2 lux Green light: 28 lux	Exposed for 4 hours every mating session for 16 weeks and 20 weeks	1. Light Box Experiment (Fluorescent light): • All light had no significant differences in the number of embryos • Spawning Rate (Likelihood of Mating): ▪ Room Light: 17.1% ▪ White Light: 14.3% ▪ Red Light: 22.9% ▪ Green Light: 20% ▪ Blue Light: 5.7% (-ve affected spawning rate) 2. iSpawn-S Experiment (LED): • Only the red light reduced embryo production; others had no significant differences in the number of embryos • Spawning Rate (Likelihood of Mating): ▪ Room Light: 46.7% ▪ Red Light: 71.4% ▪ Green Light: 62.5% ▪ Blue Light: 54.6%	Age of Zebrafish: 6-month-old wild-type (AB strain).

Zheng *et al*. [37] found that zebrafish subjected to blue light (450 nm) with an irradiance of 0.9 W/m² showed accelerated development. This was linked to increased feeding behavior and consumption, as well as improved immune responses. This was demonstrated by increased serum globulin levels, enhanced immune-related enzyme activity (lysozyme and alkaline phosphatase) in the liver and ovary, and a positive association between immune gene expression (RelA mRNA) and the protein levels of these enzymes. Gonzalo *et al*. [38] similarly discovered that blue light (472 nm) enhanced hatching rates, survival, and the expression of somatic growth factor genes, growth hormone (gh), Insulin-like growth factor 1 (igf1a), and Insulin-like growth factor 2 (igf2a). Furthermore, it reduced stress-related gene expression (CRH) and improved visual acuity, feeding efficiency, and food intake, which were attributed to the prevalence of UV- and blue-sensitive cones in the retina. Quint *et al*. [32] observed that cyan light (483 nm) significantly reduced the length of zebrafish eyes at 3 months after fertilization compared to those exposed to white light. This decrease suggests a possible regulatory influence of blue light on ocular development. Moreover, broad-spectrum daylight, encompassing blue light, facilitated normal ocular growth and mitigated UVA-induced eye damage, indicating that blue light may serve a protective function when integrated with a wide range of wavelengths.

However, exposure to blue light also has certain detrimental effects. Quint *et al*. [39] also emphasized the potential hazards linked to exposure to shorter wavelengths (425 nm), which led to minor cataracts in 12.5% of the specimens. These findings underscore the need for a meticulous examination of blue light wavelengths and their potential detrimental effects on ocular health. Subsequently, Septriani *et al*. [40] found that blue light (472 nm) at 750 lux resulted in the lowest survival rates and increased deformities, including problems with the swim bladder. Additionally, it impeded retinal pigmentation and development, reduced body length, and curtailed melatonin production, negatively impacting growth. The adverse effects were associated with mitochondrial DNA inflammation and retinal injury. In the research conducted by Cajias *et al*. [41], blue light wafound to adversely affect zebrafish spawning rate (Figure 4), with fluorescent blue light resulting in the lowest mating probability among all examined light settings (5.7%). Meanwhile, for LED blue light, the spawning rate shows a slight increase (54.6%) compared to the control group (46.7%).

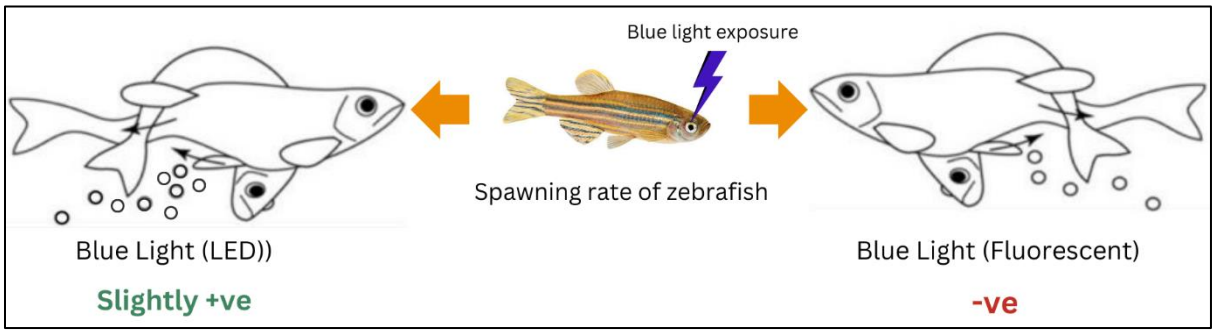

Figure 4. The effect of blue light exposure on spawning rate (Fluorescent and LED).

While several studies indicate the positive influence of blue light on zebrafish development and immune function, significant contradictions and methodological differences require careful consideration. For example, Zheng *et al*. and Gonzalo *et al*. [37, 38] found that blue light exposure can lead to faster growth, enhanced immune system activity, higher hatching rates, and increased expression of growth factors. These findings indicate that blue light, especially in the 450–472 nm range, can stimulate physiological and developmental processes. This effect could be mediated by retinal photoreceptor activation and increased feeding behavior. Conversely, other research

indicates that blue light may also have harmful effects. Septriani *et al*. [40] found that exposure to blue light at 472 nm and 750 lux led to lower survival rates, more malformations, and slowed down retinal development. These effects are associated with mitochondrial DNA damage and retinal inflammation. Cajias *et al*. [41] obtained different results under fluorescent blue light and LED blue. The differences likely stem from variations in light intensity and spectrum. Fluorescent lights emit a broader range of wavelengths that may overstimulate or stress zebrafish, while LEDs provide more controlled, narrow wavelengths that better mimic natural cues [42]. These factors can affect behavior and result in varying outcomes between the two setups. Quint *et al*. [39] emphasized the risks associated with specific wavelengths, noting that shorter blue wavelengths, such as violet light (425 nm), can cause eye damage, including cataracts. Additionally, they noted that cyan light (483 nm) affects the length of the eye. The different outcomes may result from variations in experimental parameters, such as wavelength specificity, light intensity, and the type of light source used (fluorescent vs. LED). These factors can significantly influence the observed results, potentially leading to discrepancies in data interpretation. As researchers refine their methodologies, understanding these variables becomes crucial to achieving consistent, reliable outcomes.

Overall, these studies underscore the complexity of blue light's biological effects on zebrafish, underscoring the need for standardized protocols and comprehensive assessments across multiple developmental stages and light conditions to clarify its dual roles in promoting growth and inducing damage.

3.3. Blue light effects on the neuronal and behavioral responses of zebrafish.

Blue light exposure influences the neurological and behavioral responses of zebrafish. Research indicates that blue light stimulates neurogenesis and increases attentiveness and arousal. Nevertheless, it also interrupts their sleep patterns and elevates stress levels, underscoring the intricate and conflicting impacts of blue light exposure on their physiology and behavior (Table 4).

Table 4. Blue light effects on zebrafish neurology and behavior.

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
[43]	Blue Light:480nm Green Light:560nm	Blue light: 15lux Green light: 200lux	7 days	BL: • Enhances the expression of clock genes • activates neurogenic pathways in ZEM-2S cells. • Melanopsin and other opsins mediate the effects of blue light, leading to increased intracellular calcium and modulation of neurogenesis.	Age of Zebrafish Used: Between 8 months and 1 year old
[44]	Blue light:470 nm Red light: 627 nm	400 µW	30 minutes	BL: • Activates hcrt: ChR2-EYFP • Increased locomotor activity and enhanced arousal. • Significant reduction in sleep and increased wakefulness. • RL: • No activation of hcrt: ChR2-EYFP • Normal locomotor activity and sleep cycle	Age of Zebrafish: 5 or 6 dpf. hcrt: ChR2-EYFP is a transgenic construct used in optogenetic experiments
[45]	Halogen light	26.1 mW/cm²	2 hours	VL:	Age of Zebrafish Used: 2 dpf to 6 dpf.

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
	Violet light: 410 - 426nm UV light: 350nm-400nm Blue light: 450-490nm			• Significantly increased physiological responses: Elevated heart rate, increased locomotor activity, and enhanced pectoral fin beating. • A notable heart rate increase was observed within 2 seconds of exposure BL: • Reduction in plasma melatonin levels • Increased the activity of brain centers associated with cognitive functions more • Did not stimulate heart rate and locomotor responses as quickly as violet light. UVL: • Induced a stronger locomotor response • Less effective in stimulating heart rate and pectoral fin beating compared to violet light.	
[46]	Violet: 415 nm Royal blue: 455 nm Blue: 490 Green: 530 nm Lime: 565 nm Amber: 595 nm Deep red: 660 nm Far red: 730 nm Cold white light and warm white light	LEDs: 50 µW/cm² White: 30–50 lux	10 minutes	BL: • Elicited stronger motor responses • Robust activation in the habenula, a key limbic brain region. Evidence suggests activation of non-visual melanopsin signaling, which contributes to increased motor output. GL: • Balanced behavioral • Showed functional relevance in modulating motor performance RL: • Reduced motor responses • Attenuated search behavior performance • Weaker activation of the habenula • Diminished arousal states WL: • Served as a baseline for typical search behavior patterns. • Likely integrates signals from across the retina • Produce balanced behavioral outputs	Age of Zebrafish: 6 to 7 dpf
[47]	Light Type: Blue light (475 nm)	N/A	N/A	BL: • Blue light-activated Gal4mpn354 neurons • Increased prey-like stimuli • Gal4mpn354 neurons help process approach and avoidance pathways in the tectum No light: • Shows the normal ecological and survival strategies of zebrafish without external manipulation	Age of Zebrafish: Primarily at 7 dpf.
[48]	Natural daylight: 300–700 nm. Blue light: 450–490 nm. Red light: 650–700 nm.	N/A	1 hour of exposure before brain sample collection.	BL: • Zebrafish showed a clear preference for blue light environments. • Lower levels of epinephrine (E) and norepinephrine (NE) were observed. • Decreased serotonin (5-HT) RL:	Adult wild female Danio rerio of approximately the same age and size were used.

Citation	Wavelength	Intensity	Duration of exposure	Finding	Remarks
				• Induced significant stress, reflected by elevated epinephrine (E) levels • Higher mortality rates NL: • Moderate neurotransmitter levels indicate a balanced physiological response. • No significant signs of stress were observed.	
[49]	Violet:400–440 nm Blue: 442–506 nm Green: 503–584 nm Orange:569–621 nm Red: 620–682 nm White:400–700nm	4×10^{18} photons $m^{-2}s^{-1}$	A 1-hour light pulse was given at midnight	VL: • Persistent increased activity • Partial sleep rebound • Moderate sleep fragmentation • Reduced freezing behavior BL: • Persistent increase in activity • Suppressed sleep rebound • Reduced freezing behavior GL: • Moderate sleep rebound • Sleep fragmentation • Persistent increased activity OL: • Some sleep rebound • No significant effect on activity RL: • Persistent lower swimming speed • Moderate sleep rebound • High sleep fragmentation WL: • Suppressed sleep rebound • Persistent lower freezing behavior • Strong activity	Adult wild-type zebrafish (3.3 cm in length, weighing 0.3 g) were used in the study.
[50]	UV: 365 nm Blue: 420 nm, 470 nm Green: 500 nm, 520 nm Yellow: 590nm Red: 620 nm, 635 nm, and 660 nm white light: dual peaks at 450 nm and 590 nm.	Nighttime ALAN: 20 lux Daytime:3000 lux. Natural night light 0.03 lux (approximating moonlight).	10 consecutive days of exposure to ALAN.	F0 Zebrafish (Adult Behavior): • Exposure to shorter wavelengths caused the most pronounced anxiety-like behaviors • Including increased wall-hugging and reduced movement. F1 Zebrafish (Offspring Behavior): • Exhibited reduced movement distances and lower activity levels • The transgenerational effects indicate that maternal stress caused by ALAN	-

Figure 5 shows the summary of findings for blue light effects on neural and behavioral aspects of zebrafish. Extensive research has been conducted on the substantial impact of blue light exposure on zebrafish behavior, physiology, and neurogenesis. Lindsey *et al*. [43] demonstrated that blue light stimulates neurogenic pathways, leading to the proliferation and survival of stem/progenitor cells in sensory processing regions. This effect is facilitated by melanopsin and other opsins, which elevate intracellular calcium levels and regulate neurogenic responses. Singh *et al*. [44] emphasized the role of blue light in the activation of hypocretin (Hcrt) neurons, which leads to a boost in zebrafish's movement and heightened arousal. The effect is primarily influenced by norepinephrine signaling. According to the findings of Contreras *et al*. [45], blue light dramatically decreased plasma melatonin levels while simultaneously increasing brain activity, as evidenced by increased heart rate and locomotor activity. This finding suggests that blue light plays a role in improving alertness and cognitive function. Similarly, Waalkes *et al*. [46]found that blue light elicited robust motor responses and enhanced search behavior, likely via melanopsin

signaling and activation of the habenula, an important region of the limbic brain. The findings collectively illustrate the beneficial effects of blue light on neurogenesis, behavioral arousal, and cognitive processes in zebrafish.

Furthermore, Barker and Baier [47] illustrated that blue light stimulated Gal4mpn354 neurons in zebrafish larvae, increasing their innate urge to pursue tiny prey-like entities. This discovery underscores the effects of blue light on behavioral bias via neuronal activation, particularly by regulating approach and avoidance pathways in the tectum. The lack of blue light hindered the activation of these neurons, reducing the zebrafish's capacity to identify small objects as prey. Lastly, S and Inbaraj [48] indicated that zebrafish favored blue light environments because it resembles their natural habitat, and the findings indicate diminished physiological stress, proven by the lower levels of epinephrine and norepinephrine, implying that blue light exerts a calming influence, while reduced serotonin levels suggest its role in stress modulation.

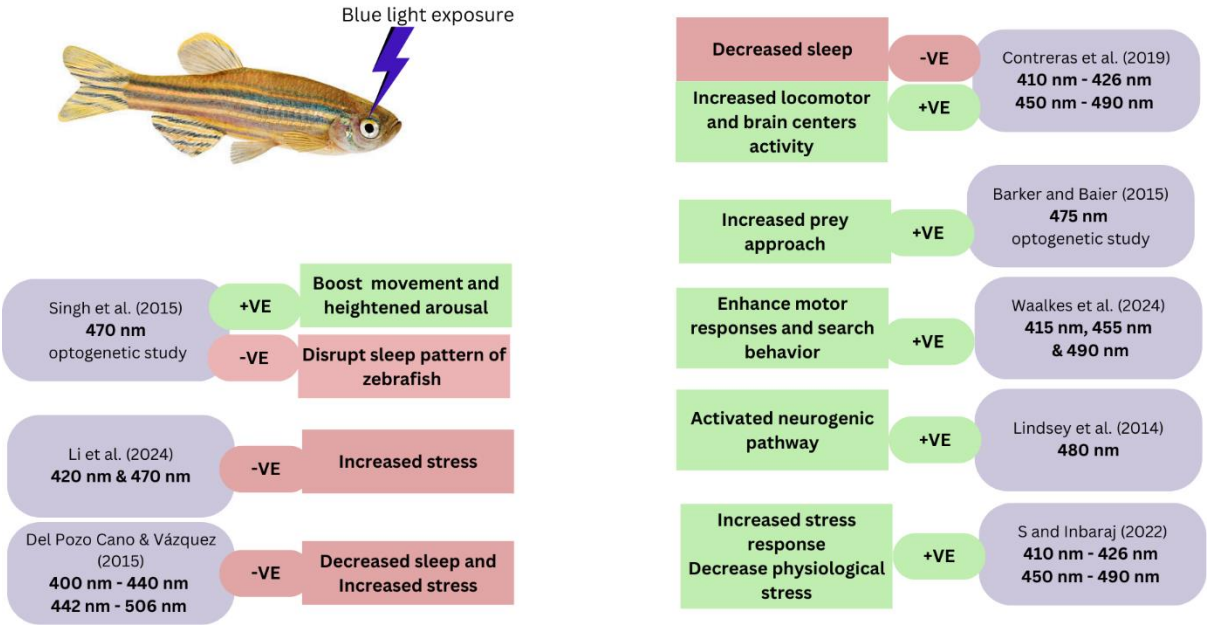

Figure 5. Findings summarization of the blue light study on the neuronal/behavioral aspects of zebrafish.

Despite its beneficial effects, blue light exposure also has several negative effects, particularly on stress and behavioral disruption. Del Pozo Cano and Vázquez [49] found that blue light enhances swimming speed and distance, modifies freezing behavior and vertical orientation, indicating higher activity and spatial alterations. This indicates that the stress level in zebrafish is increased when exposed to blue light. Li *et al*. [50] found that blue light triggered anxiety-like behaviors in adult zebrafish, characterized by heightened wall-hugging (zebrafish swimming near the edges of the aquarium or tank) and reduced movement. The effects observed were accompanied by transgenerational consequences: offspring of mothers exposed to blue light showed reduced activity and shorter movement distances, underscoring the potential long-term impacts of blue light exposure on zebrafish populations. Furthermore, although Contreras *et al*. [45] observed a decrease in melatonin level and an improvement in behavioral activity when exposed to blue light, this disruption of melatonin regulation may affect sleep patterns. These findings indicate that blue light may positively influence zebrafish behavior and physiology; it can concurrently produce adverse effects, including heightened stress levels, despite observed behavioral improvements. This emphasizes the dual character of blue light exposure, wherein advantageous benefits on behavior may coexist with adverse effects on general well-being.

While several research studies indicate that blue light influences zebrafish neurology and behavior, a critical analysis reveals that these effects are not always advantageous and often depend on specific experimental conditions. For example, Lindsey *et al*. and Singh *et al*. [43] both found that blue light increased the growth of new brain cells and activity levels, but they used very different types of zebrafish: adult zebrafish and 5–6 day old larvae, which could explain the differences in how they respond to light and how their brains adapt. Moreover, while studies such as Waalkes *et al*. and Barker and Baier [46, 47] show that activating motor pathways and certain brain circuits can be helpful, other research questions this overall positive view. Del Pozo Cano and Vázquez and Li *et al*. [49, 50] found that prolonged exposure to blue light can cause serious problems like sleep issues, anxiety-related behaviors, and effects that can be passed down to future generations, suggesting that this exposure is harmful. Differences in methodologies, such as intensity, exposure duration, and zebrafish age, also contribute to divergent findings. While some studies view increased activity as an indication of cognitive enhancement or alertness, others caution that such behavior could signify elevated stress levels. Thus, rather than presenting a consistently beneficial or harmful profile, blue light has multifaceted, sometimes contradictory effects on zebrafish, depending on factors such as age, light conditions, and neurophysiological endpoints. A more nuanced interpretation is essential to fully understand the implications of blue light exposure on zebrafish health and behavior.

3.4. Blue light effects on clock gene/circadian rhythms of zebrafish.

Multiple studies consistently emphasized the substantial influence of blue light at 450–470 nm on the circadian rhythm of zebrafish (Table 5). Blue light has been demonstrated to significantly influence the resetting and regulation of the circadian clock in zebrafish cells and larvae. Ramos *et al*. [51] discovered that blue light (450 nm – 470nm) with intensity 87.85-95.17mW/cm² proficiently re-establishes the expression of circadian clock genes, including per2 and cry1a, in ZEM-2S cells after brief exposure (10 minutes) of blue light. This process is facilitated by signaling pathways, such as the phosphoinositide pathway (PLC), calcium signaling, and the MAPK pathway, with melanopsins like Opn4 being pivotal. Di Rosa *et al*. [52] similarly discovered that zebrafish larvae subjected to blue light (465 nm) exhibited earlier activity rhythms at 4 dpf than those under alternative light settings. The rhythmic expression of clock genes, including per1b, per2, and dbp, was observed as early as 3 dpf under blue light, with clock1 rhythms emerging by 7 dpf. Pagano *et al*. [53] similarly observed that blue light (peak wavelength 468 nm) swiftly generates ROS within 5 minutes, reaching a peak after 1–2 hours. This resulted in bimodal activation of MAP kinases (p38 and JNK), highlighting the strong impact of blue light on ROS-mediated signaling pathways. Ramos *et al*. [51] observed that blue light-induced ROS and reactive nitrogen species (RNS) may affect the regulation of clock genes, emphasizing the dual function of oxidative stress in responses to blue light.

Table 5. Blue light effects on zebrafish clock gene/circadian rhythms.

Citation	Wavelength	Intensity	Duration of exposure	Finding (result of the study)	Remarks
[51]	Blue light: 450–475 nm	87.85 to 95.17 mW/cm²	Protocol 1: 10 minutes of blue light on day 7. Protocol 4: 1, 5, and 10 minutes of blue light exposure.	BL: • Effectively resets clock gene expression • Activate calcium release and downstream signaling. • The role of cAMP remains ambiguous but partially contributes to light-induced gene regulation. • Light-induced ROS and RNS may play roles in clock gene modulation.	The study does not involve whole zebrafish organisms but focuses on cultured cells.

Citation	Wavelength	Intensity	Duration of exposure	Finding (result of the study)	Remarks
[52]	White light: Full visible spectrum Blue light: Peak 465nm Red light: Peak 639nm	1.62 E+18 photons m^{-2} s^{-1}	7 days.	BL • Larvae under blue light developed daily activity rhythms earlier at 4 dpf • Early rhythmic expression of per1b, per2, and dbp was observed at 3 dpf. • Clock1 rhythmic expression appeared by 7 dpf. RL: • Activity rhythms appeared later, at 5 dpf. • lower overall • The rhythmicity of clock genes developed more slowly WL: • Activity rhythms appeared at 5 dpf • Rhythmicity of per1b, per2, and dbp started at 3 dpf; Clock1 and bmal1 showed rhythmic expression by 7 dpf. • Larvae showed high overall activity.	Age of Zebrafish Used: 0 to 7 dpf
[53]	White LED Blue LED: peak 468 nm Red LED: peak 657 nm	N/A	3 days.	BL: • ROS Levels increase rapidly within 5 minutes, • Bimodal activation of p38 and JNK • Significant induction of cry1a and per2 via the D-box enhancer. RL: • No significant increase in ROS. • Minimal activation of p38 and JNK compared to blue light. • Induction of cry1a and per2 WL: • ROS levels are intermediate compared to blue light. • Moderate activation of p38 and JNK. • Induction of cry1a and per2	Age of Zebrafish Used: 6hpf and 26 hpf

While the overall evidence indicates that blue light strongly influences the zebrafish circadian system, a closer look at the methods used reveals key differences that affect how we interpret the results. A key contrast lies in the biological models used: Ramos *et al*. [51] studied ZEM-2S cell cultures to look at how signals move inside cells, including calcium flow and the effects of ROS and RNS, whereas Di Rosa *et al*. and Pagano *et al*. [52, 53] studied whole embryos or larvae, which allowed them to incorporate behavioral and systemic responses. This difference raises questions about the translatability of cellular responses to whole-organism effects. Additionally, while all three studies report upregulation of core clock genes like per2 and cry1a, the pathways through which this occurs diverge. Ramos *et al*. [51] highlight the phosphoinositide and MAPK pathways in lab-grown cells, while Pagano *et al*focus on how ROS activates kinases in developing embryos, suggesting that blue light might trigger similar yet distinct molecular processes depending on the developmental stage or the model used. Additionally, while Di Rosa *et al*. [52] describe blue light as promoting earlier onset of behavioral rhythmicity and gene oscillation, Pagano *et al*. [53] caution that prolonged exposure to blue light may increase ROS levels, which could lead to oxidative stress. This nuance is not addressed in Di Rosa's extended 7-day exposure timeline. The identified discrepancies call for standardized light exposure protocols and further investigation into dose-response thresholds. While the overall findings are complementary, a critical synthesis reveals methodological differences that may lead to subtle inconsistencies. Future research design should address these issues.

4. Discussion

4.1. Blue light effects on oxidative stress of zebrafish.

Oxidative stress occurs when the balance between ROS and antioxidants is disrupted, favoring ROS and leading to cellular damage and disruption of redox signaling [54]. ROS encompassing free radicals such as superoxide and hydroxyl radicals, as well as non-radicals like hydrogen peroxide, are generated during standard metabolic activities, especially within the mitochondria [55]. However, their overproduction may arise from external influences such as pollution, radiation, and toxins. Accumulated ROS harms cellular constituents, including DNA, lipids, and proteins, potentially resulting in mutations, compromised membrane integrity, and disturbed enzymatic activity [56]. Antioxidants, including enzymatic defenses such as superoxide dismutase, catalase, and glutathione peroxidase, as well as dietary antioxidants, neutralize ROS, safeguard cells, and maintain oxidative balance [57]. Exposure to blue light markedly elevates the generation of ROS in retinal and corneal cells via photochemical processes. Increased amounts of reactive oxygen species, particularly superoxide anions and hydrogen peroxide, lead to oxidative stress and cellular injury, resulting in lipid peroxidation, protein oxidation, and DNA damage [58].

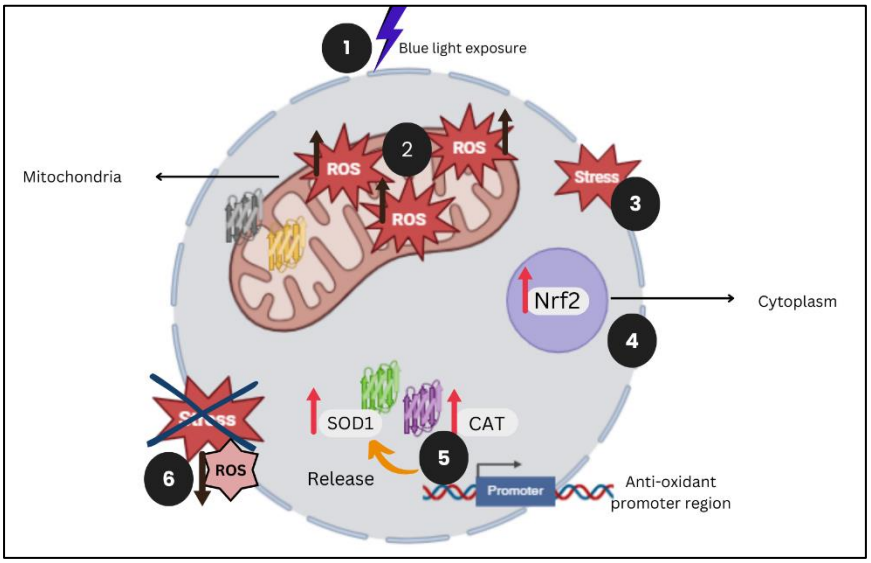

Figure 6. Antioxidant gene under exposure to blue light.

Exposure to blue light has been shown to reduce oxidative stress by promoting specific antioxidant mechanisms at the genetic level [59]. This aspect has been extensively investigated in zebrafish, where blue light modulates the expression of genes involved in antioxidant synthesis and cellular defense (Figure 6). Previous studies indicate that blue light can enhance the expression of genes encoding antioxidant enzymes, such as superoxide dismutase (SOD) and CAT [30,32]. These enzymes are often increased during oxidative stress as they are essential for detoxifying ROS. The activation of these genes is facilitated by the interaction of blue light with photoreceptors, which initiate signaling pathways that increase antioxidant defense systems [60]. The interaction of blue light with cellular photoreceptors, including cryptochromes and opsins, initiates a series of intracellular signaling pathways. A crucial mechanism entails the activation of the nuclear factor erythroid 2–related factor 2 (NRF2), a transcription factor recognized for its pivotal function in the oxidative stress response. In typical circumstances, NRF2 is bound with its inhibitor, Kelch-like ECH-associated protein 1 (KEAP1) in the cytoplasm, which makes it inactive [61]. However, blue light-induced signaling or oxidative stress can disrupt this mechanism, thereby facilitating the nuclear translocation of NRF2. Upon NRF2 entering the nucleus, it will

bind to antioxidant response elements (AREs) located in the promoter regions of target genes, such as SOD and CAT. This binding triggers the transcription of genes, resulting in the synthesis of enzymes that neutralize ROS [60]. SOD catalyzes the superoxide anion (O_2^-) and converts it to hydrogen peroxide (H_2O_2), which eventually breaks down by catalase or glutathione peroxidase (GPx) into water (H_2O) and oxygen (O_2) [60,62]. This series of reactions is crucial for reducing oxidative damage and maintaining cellular integrity [62]. The NRF2-mediated response is especially important in the context of blue light exposure because it underscores how blue light can both induce oxidative stress and trigger defense mechanisms to mitigate its effects. These results highlight the intricate relationship among blue light, ROS generation, and antioxidant pathways that provide protection.

Conversely, redundant exposure to blue light has been associated with detrimental effects on oxidative stress and cellular health, especially in sensitive tissues such as the retina [61]. While short-duration exposure to blue light can activate protective antioxidant mechanisms, extended exposure usually leads to oxidative damage and cellular malfunction by overpowering the defense mechanism (Figure 7). The retina is especially vulnerable due to its high metabolic activity, abundance of photoreceptors, and mitochondrial density [63]. Research on zebrafish larvae has shown that prolonged exposure to blue light causes the retinal layers to thin, increases DNA damage markers, such as phosphorylated histone H2AX (γ-H2AX), and increases the expression of apoptotic proteins, including caspase-3 [35,16]. As a biological response to injury, γ-H2AX foci formed due to oxidative damage to nuclear DNA caused by ROS production, and, at the same time, the apoptotic signaling pathway was activated [64]. In the apoptotic pathway, when ROS levels are high, it disrupts mitochondrial membrane potential, leading to the release of cytochrome c into the cytoplasm. Cytochrome c initiates caspase-9 activation, which subsequently leads to caspase-3 activation, which is recognized as the principal executioner caspase. Caspase-3 cleaves multiple cellular substrates, resulting in DNA fragmentation, chromatin condensation, and ultimately, cell death [65]. In addition, prolonged exposure to blue light generates reactive molecules that can disrupt cellular homeostasis by oxidizing lipids, proteins, and DNA. Initially, cells activate NRF2-mediated antioxidant pathways to prevent oxidative stress. However, these defense mechanisms are likely to fail when ROS generation becomes chronic or above the crucial threshold [16].

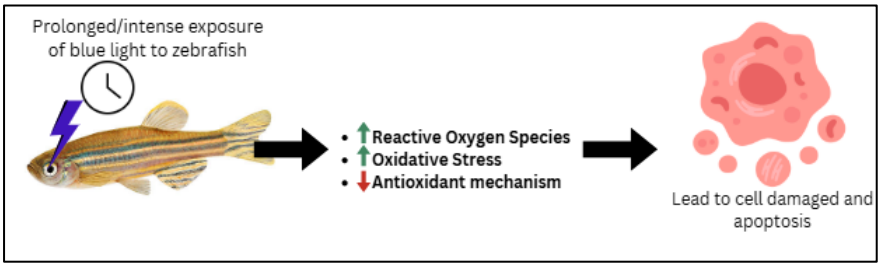

Figure 7. Prolonged/intense exposure to blue light in zebrafish.

In conclusion, whereas blue light may positively influence oxidative stress by augmenting defense mechanisms and antioxidant activity, excessive exposure may result in significant cellular damage. The balance between these contrasting effects is essential for comprehending the impact of blue light on retinal health in zebrafish and different species.

4.2. Blue light effects on the development of zebrafish.

Zebrafish serve as a prominent model organism for developmental biology owing to their rapid, transparent embryonic development. Zebrafish undergo specific developmental stages from

fertilization to hatching, namely zygote, cleavage, blastula, gastrulation, segmentation, and pharyngula, all during the initial three days following fertilization [66]. This rapid advancement enables researchers to monitor organogenesis and morphological alterations in real time, making zebrafish an exemplary model for examining genetic and environmental influences on development.

Exposure to blue light has shown substantial benefits for zebrafish development, especially when administered under controlled conditions. At the molecular level, exposure to blue light has been associated with the overexpression of growth-related genes, including insulin-like growth factor 1a (igf1a) and insulin-like growth factor 2a (igf2a). These genes are essential for cell regulation, proliferation, differentiation, and tissue development (Figure 8) [67]. Insulin-like growth factor (IGF) signaling plays a vital role in embryonic and larval development, regulating somatic growth, organogenesis, and metabolism. The increased expression of these genes in response to blue light suggests that this wavelength activates critical signaling pathways for growth, likely via photoreceptors that are sensitive to blue light [68].

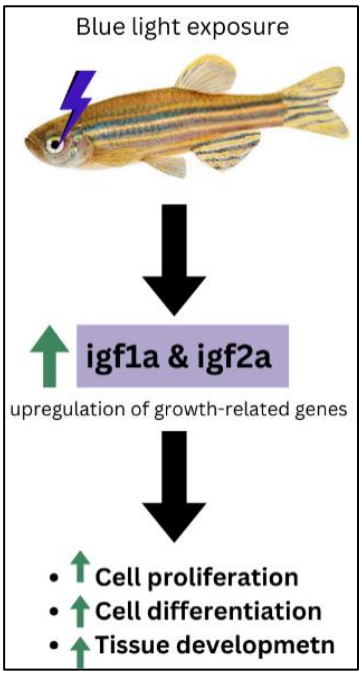

Figure 8. Blue light affects growth-related genes.

Enhancement of somatic growth factor gene expression, such as gh, igf1a, and igf2a, is associated with increased growth and survival rates [38]. Fish exposed to blue light demonstrate improved growth and immune function, attributable to physiological and molecular mechanisms influenced by the specific properties of blue light [69]. The enhanced growth is associated with increased appetite and elevated feed intake (FI), potentially influenced by blue light's effects on circadian rhythms and the regulation of appetite-related hormones such as ghrelin and leptin. The increase in serum globulin levels indicates enhanced immune defenses, reflecting a more robust humoral immune response [37]. Immune-related enzymes, including lysozyme (LZM) and alkaline phosphatase (AKP), exhibit increased activity in response to blue light. These enzymes play a vital role in pathogen defense and the modulation of immune responses [70]. Additionally, blue light affects immune gene expression, as evidenced by a positive correlation between elevated RelA mRNA levels and LZM and AKP protein expression [37].

Conversely, blue light can also negatively impact development, as evidenced by a past study showing that zebrafish embryos exposed to blue light had the lowest survival rates among

lighting conditions, with increased deformations and swim bladder abnormalities [40]. The suppression of eye pigmentation and retinal development by blue light exposure raises substantial concerns about its potential to cause retinal damage, particularly through mitochondrial dysfunction and inflammatory responses [71]. Investigations using zebrafish, an important model for studying retinal health, have revealed that prolonged exposure to blue light can alter retinal morphology, delay photoreceptor maturation, and impair vision [72]. Furthermore, exposure to blue light markedly suppressed growth in axial length and head size in larvae, consistent with its effect on diminished retinal development [39]. Axial length denotes the distance from the front (cornea) to the posterior (retina) of the eye. It is a crucial factor in assessing the optical power and focus of the eye [73]. A correctly aligned axial length guarantees that light entering the eye focuses accurately on the retina, producing clear vision. An excessively long axial length results in myopia, characterized by blurred vision of distant objects [74]. In contrast, if it is excessively short, it results in hyperopia (farsightedness), causing proximal objects to appear out of focus [75]. Axial length decreased by exposure to blue light through mechanisms that presumably engage retinal signaling and refractive modulation. It can induce dopamine release in the retina, a neurotransmitter recognized for its role in inhibiting ocular elongation via modulating scleral remodeling and growth [76].

In summary, exposure to blue light in zebrafish exhibits both beneficial and harmful consequences. Positively, it promotes growth, immune function, and the expression of growth-related genes, thereby enhancing development and survival. Prolonged exposure to blue light may lead to developmental complications, including delayed retinal growth, swim bladder anomalies, and possible retinal injury due to mitochondrial malfunction. Blue light also influences axial length, potentially leading to refractive errors such as myopia or hyperopia. These findings indicate that although blue light promotes growth and immune function, its effects on eye development and vision warrant further examination to understand the long-term implications.

4.3. Blue light effects on neuronal/behavioral responses of zebrafish.

During the larval stage, zebrafish exhibit many behaviors, including swimming, sensory responses, and reflexes, indicating their neurological development [77]. Their nervous system exhibits structural similarities to that of other vertebrates, containing essential neurotransmitter systems such as dopamine, serotonin, and GABA, which are vital for behavioral regulation [78]. The capacity to visualize brain circuits in vivo enables researchers to associate neuronal processes with behavioral outcomes, rendering zebrafish an invaluable resource for examining the neural foundations of behavior and for investigating the effects of diverse stimuli on their neurological well-being [78].

Exposure to blue light has demonstrated considerable beneficial effects on neuronal and behavioral responses in zebrafish, chiefly by augmenting neurogenic plasticity and stimulating essential pathways involved in sensory processing. Blue light exposure enhanced the expression of circadian genes and stimulated neurogenic pathways mediated by melanopsin and other opsins [46]. These effects facilitated the survival and proliferation of stem cells in sensory structures, emphasizing their role in fostering neurogenesis [43]. Furthermore, blue light serves as a stimulus for activating neurons in optogenetic assays. For instance, blue light stimulated Gal4mpn354 neurons, promoting approach behaviors towards prey-like cues, emphasizing its significance in regulating approach-avoidance circuits in the tectum [47]. Additionally, blue light facilitates the activation of hypocretin (Hcrt) neurons, which play a role in enhancing alertness and locomotor activity [79]. This stimulation results in enhanced alertness and greater locomotion in zebrafish.

The research showed that norepinephrine (NE), a neurotransmitter linked to arousal and alertness, has a vital downstream function in this process. Zebrafish possessing functional NE signaling exhibit marked decreases in sleep and increased wakefulness in the presence of blue light, indicating that NE is crucial for the arousal effects facilitated by Hcrt neurons [79]. Upon exposure to blue light, the ChR2 channel activates, permitting the influx of positively charged ions, including sodium (Na^+) and calcium (Ca^{2+}), into the neuron. The inflow of ions induces depolarization in the neuron, hence initiating its activation. The specificity of ChR2 for blue light renders it an ideal instrument for optogenetic research, enabling researchers to regulate neuronal activity with light [79] accurately.

In neural research, while blue light enhances zebrafish behavior by augmenting swimming speed, sensory response, and reflective behavior, it may also produce adverse effects. The elevated swimming velocity and activity may signify higher arousal or stress responses. This indicates that exposure to shorter wavelengths may not only enhance physical activity but also elicit a stress response in zebrafish [50]. Additionally, sleep cycle disruption is concerning, as sleep is essential for sustaining healthy physiological and neurological processes. Light exposure-induced sleep suppression may disrupt normal circadian rhythms, altering zebrafish overall health and behavior and potentially confounding outcomes in long-term research [49].

In summary, blue light exposure markedly affects zebrafish behavior and neural function, facilitating neurogenesis, improving sensory processing, and stimulating essential pathways related to alertness and motor responses. Stimulation of the melanopsin and opsin pathways promotes neurogenic plasticity, leading to heightened arousal, motility, and sensory responses. The function of blue light in influencing approach-avoidance behavior and arousal circuits highlights its potential utility in optogenetic research. Nonetheless, despite these beneficial effects, blue light exposure can pose potential disadvantages, including the induction of stress responses, disruption of sleep cycles, and increased oxidative stress, which can adversely impact neuronal function and overall health.

4.4. Blue light effects on circadian/clock gene of zebrafish.

Circadian rhythms are innate, approximately 24-hour cycles that regulate numerous physiological and behavioral processes in organisms and arenfluenced by internal biological clocks [80]. The rhythms are governed by a sophisticated network of clock genes involved in transcription-translation feedback loops (TTFLs), enabling organisms to align their biological operations with external environmental signals, including light and temperature. The primary pacemaker in mammals is the suprachiasmatic nucleus (SCN), which regulates the timing of peripheral clocks throughout the body [80,81]. Zebrafish have become an important model for investigating circadian rhythms due to their transparent embryos and rapid development. They have a well-defined circadian clock that resembles mammalian systems, featuring essential clock genes such as clock, bmal1, period, and cryptochrome [82]. Studies indicate that zebrafish exhibit specific circadian behaviors, including variations in locomotor activity and feeding behavior, which are affected by light cycles. Their capacity to adapt to different light conditions makes them an ideal model for exploring the molecular underpinnings of circadian rhythms and their effects on behavior and physiology [83].

Exposure to blue light was found to have a strong, robust impact on the regulation of clock genes, particularly period circadian regulator 2 (PER2) and cryptochrome circadian regulator 1a (CRY1a). This suggests that blue light is a potent inducer of circadian rhythm regulation, resetting the molecular clock [51,52]. PER2 and CRY1a are key regulators of circadian rhythms, the 24-

hour biological cycle. PER2 regulates gene expression in the molecular clock, while CRY1a represses CLOCK and BMAL1 transcription factors to maintain rhythmic oscillations, impacting sleep, metabolism, and hormone regulation [84,85]. Table 6 highlights the core circadian rhythm genes involved in the molecular clock and their responses to blue light. Blue light serves as a powerful environmental cue that activates or regulates these genes, particularly PER2 and CRY1a.

Table 6. Blue light effects on core circadian genes.

Gene	Function	Effect of Blue Light
Period Circadian Regulator 2 (**PER2**)	Regulates gene expression in the molecular clock	Strongly increased; it helps reset circadian rhythms.
Cryptochrome Circadian Regulator 1a **(CRY1a)**	Represses CLOCK and BMAL1 to maintain rhythmic oscillations	Activated by blue light; refines circadian rhythm timing
Circadian Locomotor Output Cycles Kaput **(CLOCK)**	Forms a transcriptional complex with BMAL1 to activate circadian genes	Activated indirectly via light signaling pathways
Brain and Muscle ARNT-Like 1 **(BMAL1)**	Partners with CLOCK to regulate the expression of clock genes via E-box binding	Activated via light signals; initiates circadian gene expression

Further evidence that blue light plays a role in fostering synchronized biological rhythms is provided by the early rhythmic expression of per1b and per2, detected as early as 3 dpf [52]. Apart from that, when it comes to entraining circadian rhythms, blue light is particularly effective. This is because it has the power to activate specific photoreceptors. An example of one of these photoreceptors is melanopsin, which is found not only in the retina of zebrafish but also in several peripheral organs [86]. This activation leads to the expression of core clock genes, which are crucial for maintaining circadian rhythms and facilitating the synchronization of physiological processes with environmental light-dark cycles.

Blue light exposure causes oxidative stress, characterized by a rapid rise in ROS, activating two distinct phases of stress-related proteins: an initial acute response and a persistent phase [50]. The oxidative stress response is intricately linked to the regulation of circadian rhythms, as demonstrated by the activation of circadian genes cry1a and per2 via the D-box enhancer mechanism [45]. ROS and stress-related signaling proteins function as intermediates, linking oxidative signals to alterations in circadian gene expression [52,57]. These findings underscore the dual function of blue light as a stressor and a regulator of circadian rhythms, providing insights into its effects on cellular health and the biological clock.

Overall, the ability of blue light to accelerate rhythmic behavior and induce robust gene expression in larvae is a promising discovery, suggesting it may be used to manipulate circadian rhythms at the organismal and cellular levels.

5. Conclusions

Overall, blue light significantly influences zebrafish physiology, presenting both considerable advantages and potential hazards contingent on exposure conditions. Studies indicate that blue light facilitates growth, improves defense mechanisms, improves neuronal and behavioral function, and modulates circadian rhythms. These benefits are facilitated by processes including the activation of antioxidant enzymes, stimulation of neurogenesis, and synchronization of clock genes. Excessive or prolonged exposure to blue light can induce oxidative stress, apoptosis, and altered circadian regulation, underscoring its dual nature. Blue light's impact is unique and more prominent in comparison to other wavelengths. While current studies provide valuable insights into the biological effects of blue light, they are often constrained by methodological limitations such as inconsistent light intensities and varying exposure durations. These inconsistencies hinder the ability to draw definitive conclusions across studies. Future research should aim to standardize experimental conditions and focus on specific wavelengths and

light intensities. Using zebrafish as a model, future studies should also investigate the complete mechanistic pathway from light exposure through oxidative stress, mitochondrial disruption, and cellular damage to develop a clearer understanding of the full impact of blue light. Such comprehensive findings could then be translated to understand better the potential effects of blue light exposure in humans.

Author Contributions

Conceptualization, I.Z.H. and S.A.R.; methodology, I.Z.H. and R.D.; validation, I.Z.H., S.A.R., R.D., F.I.S.A., and N.F.N.M.I.; data curation, I.Z.H., S.A.R., and R.D.; writing original draft preparation, I.Z.H., S.A.R and R.D.; writing review and editing, I.Z.H., S.A.R., R.D., F.I.S.A., and N.F.N.M.I.; visualization, I.Z.H; supervision, S.A.R. and R.D. All authors discussed the results and commented on the manuscript. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

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Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

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