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Peripheral neuroprotective potential and toxicological profile of fascaplysin in zebrafish models

Ki-Hoon Park[1,2], Youngbuhm Huh[1,3,4], Hyung-Joo Chung[2], Hiroyuki Konishi[5,6], Junyang Jung[1,3,4], Na Young Jeong[7]

[1]Department of Anatomy and Neurobiology, College of Medicine, Kyung Hee University, Seoul, [2]Department of Anesthesiology and Pain Medicine, College of Medicine, Kosin University, Busan, [3]Department of Biomedical Science, Graduation School, Kyung Hee University, Seoul, [4]Department of Precision Medicine, College of Medicine, Kyung Hee University, Seoul, Korea, [5]Division of Neuroanatomy, Department of Neuroscience, Yamaguchi University Graduate School of Medicine, Ube, [6]Department of Functional Anatomy and Neuroscience, Nagoya University, Graduate School of Medicine, Nagoya, Japan, [7]Department of Anatomy and Cell Biology, College of Medicine, Dong-A University, Busan, Korea

Abstract: Fascaplysin is a bioactive compound derived from marine sponges, which have anticancer properties and potential neuroprotective effects mediated by mitigation of oxidative stress-induced neurotoxicity. This study investigated the concentration-dependent effects of fascaplysin in zebrafish models, focusing on embryonic survival, cardiac function, melanocyte formation, and peripheral nerve health. Zebrafish embryos were exposed to fascaplysin at concentrations ranging from 10 nM to 100 μM, and developmental parameters were assessed. At higher concentrations (≥1 μM), fascaplysin significantly decreased embryo survival rates, delayed hatching, impaired cardiac function, and caused morphological abnormalities, including disruption of melanocyte formation and structural deformities. By contrast, lower concentrations (10 nM and 100 nM) did not exhibit significant toxicity. In adult zebrafish, fascaplysin at 100 nM reduced the expression of superoxide-producing enzymes and preserved peripheral nerve integrity following injury, as demonstrated by maintenance of fluorescence in transgenic zebrafish with expression of green fluorescent protein in Schwann cells. These findings suggest that fascaplysin exhibits peripheral neuroprotective effects at low concentrations, potentially through the reduction of oxidative stress and preservation of Schwann cell function. However, the toxicity observed at higher concentrations highlights the importance of dose optimization. Fascaplysin is a promising candidate for the development of new therapeutic strategies for peripheral neuropathies, and further studies are required to elucidate the underlying mechanisms and validate its efficacy in mammalian models.

Key words: Fascaplysin, Neuroprotection, Zebrafish, Schwann cells, Peripheral neuropathy

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Corresponding author:
Junyang Jung
Department of Anatomy and Neurobiology, College of Medicine, Kyung Hee University, Seoul 02447, Korea
E-mail: jjung@khu.ac.kr
Na Young Jeong
Department of Anatomy and Cell Biology, College of Medicine, Dong-A University, Busan 49201, Korea
E-mail: jnyjjy@dau.ac.kr

Introduction

Fascaplysin is a bioactive compound isolated from marine sponges, initially recognized for its potent anticancer properties due to strong inhibition of cyclin-dependent kinase 4 (CDK4) [1]. Beyond anticancer activity, fascaplysin has neuroprotective effects mediated by mitigation of neurotoxicity induced by oxidative stress, suggesting potential to reduce cellular damage in nervous tissues [2]. This multitarget pro-

file of action is increasingly valued for the treatment of complex diseases, such as neurodegenerative disorders, which involve multiple interacting pathological pathways [3].

In neurodegenerative conditions, multitarget drugs offer significant advantages by addressing the combined effects of oxidative stress, inflammation, and progressive neuronal loss [4]. The ability of fascaplysin to modulate several biological pathways may be particularly useful for managing oxidative stress, a major contributor to neuronal damage in such disorders. However, research on the neuroprotective effects of fascaplysin has been limited, with a notable lack of data regarding its impact on the peripheral nervous system (PNS), specifically on peripheral nerves and Schwann cells. Schwann cells are essential for myelination and repair in the PNS [5], and dysfunction of these cells has been implicated in various peripheral neuropathies. Peripheral neuropathies encompass a wide range of disorders resulting from peripheral nerves damage, leading to symptoms such as pain, numbness, and muscle weakness [6]. These conditions can result from diabetes, chemotherapy, infections, and traumatic injuries. Current treatments are mostly limited to symptomatic relief, highlighting the need for novel therapeutic agents that can protect and repair peripheral nerves. As fascaplysin can influence multiple pathways involved in neuronal survival and repair, it is a promising candidate for peripheral neuroprotection.

Assessing the developmental toxicity of potential therapeutic compounds is crucial to ensure safety, particularly for drugs targeting complex systems, such as the nervous system. Zebrafish (Danio rerio) embryo models are widely used for developmental toxicity testing due to their rapid development, transparency, and genetic similarities to human disease pathways [7]. These attributes allow efficient evaluation of effects on survival, hatching, organ function, and morphological development. Moreover, use of zebrafish embryos allows high-throughput screening of compounds, which makes them ideal for preliminary toxicity assessments.

In addition to embryonic models, studies in adult zebrafish provide valuable insights into peripheral nerve regeneration and neuroprotection in a whole-organism context. Transgenic zebrafish expressing enhanced green fluorescent protein (eGFP) in Schwann cells, such as the myelin basic protein (MBP) transgenic line, represent a robust model for examining peripheral nerve integrity and assessing neuroprotective effects following localized nerve injury [8]. This model allows direct visualization of Schwann cells and peripheral nerves, facilitating the evaluation of compounds that may enhance nerve regeneration or prevent degeneration [9].

Oxidative stress plays a significant role in peripheral nerve damage, contributing to the pathogenesis of various neuropathies [10]. Therapeutic agents targeting oxidative stress pathways can potentially prevent or mitigate nerve damage. Fascaplysin has been shown to inhibit oxidative stress markers [2], suggesting potential efficacy for protecting peripheral nerves from oxidative damage.

In this study, the concentration-dependent effects of fascaplysin were investigated in zebrafish models, focusing on embryonic survival, cardiac function, melanocyte formation, and peripheral nerve health. Survival, hatching, and cardiac outcomes were examined in embryos to assess developmental toxicity. In adult zebrafish, oxidative stress markers and peripheral nerve integrity were evaluated to determine neuroprotective effects. The aim was to clarify the potential therapeutic applications and safety profile of fascaplysin in the PNS.

By focusing on the PNS, this study addresses a gap in research regarding the effects of fascaplysin on peripheral nerves and Schwann cells. The findings may have implications for the development of new therapeutic strategies for peripheral neuropathies, offering hope for conditions that currently have limited treatment options.

Materials and Methods

Animals and reagents

All zebrafish care and maintenance procedures followed the guidelines and regulations of the Kyung Hee University Committee on Animal Research approval number #KHSASP-21-302. The zebrafish strains used in this study were AB/Tuebingen wild-type and Tg(MBP:eGFP) transgenic lines. The transgenic line was provided by the Zebrafish Center for Disease Modeling (ZCDM). Adult zebrafish were maintained at 28.5°C and fed twice daily with brine shrimp and Tetramin® Tropical Flakes (#77101; Tetra). Embryos were obtained by natural mating and raised at 28.5°C in egg water (0.3 mg/L sea salt). Fascaplysin (#341251) was purchased from Calbiochem.

Exposure of zebrafish to fascaplysin

Zebrafish embryos (4 hours post-fertilization) were exposed to fascaplysin at final concentrations ranging from 0.01 to 100 μM, assuming complete dissolution of fascaplysin in

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the aqueous medium. Embryos were exposed to fascaplysin solution for 120 hours in a waterborne setting. Live embryos were observed every 24 hours using an SMZ800 stereomicroscope and photographed using a DIGITAL SIGHT DS-Fi3 (Nikon). A total of three sets of 30 embryos were morphologically evaluated up to 120 hours of development, based on criteria outlined previously [11]. The malformation rate was calculated as the ratio of malformed embryos and/or larvae to total number of surviving embryos at each time point.

For adult zebrafish, wild-type males (8 months old) were exposed to fascaplysin at concentrations ranging from 0.1 to 10 μM. Each concentration group consisted of three sets of 3 zebrafish, and survival rates were monitored over a 10-day exposure period. Survival rates were calculated as the percentage of fish alive at the end of the exposure period relative to the initial number of fish in each group.

Analysis of oxidative stress markers in zebrafish exposed to ethanol and fascaplysin

Two groups of 12 wild-type male zebrafish (8 months old) were housed in isolated glass tanks containing 0.5% ethanol (v/v) with or without 100 nM fascaplysin for 2 days. To minimize fluctuations in ethanol concentration caused by the metabolisms of the fish and natural evaporation, the tanks were covered with glass lids. The fish were fed regular food twice daily (10 mg/fish/meal). After the exposure period, they were sacrificed and heart, liver, and brain tissues were isolated and analyzed for the expression of oxidative stress markers [12].

Real-time quantitative polymerase chain reaction

Total RNA was isolated from adult zebrafish organs using TRIzol® reagent in accordance with the manufacturer's instructions (#15596-026; Invitrogen). Complementary DNA (cDNA) was synthesized via reverse transcription using SuperScript™ III reverse transcriptase (#18080044; Invitrogen). Real-time quantitative polymerase chain reaction (RT-qPCR) was conducted on a thermal cycler (TP700; Takara) with 45 cycles, using 50 ng cDNA, 200 pmole/μL gene-specific primers (Supplementary Table 1), and TB green premix Ex Taq (#RR420A; Takara). *gapdh* was used as the reference gene, and relative quantification was performed using the double-delta $\Delta\Delta C_t$ method [13]. Each RT-qPCR assay was performed in triplicate.

Adult zebrafish model of peripheral nerve degeneration in the caudal fin

To induce peripheral nerve injury, zebrafish were anesthetized with 0.6 mM tricaine (ethyl 3-aminobenzoate methanesulfonate, #E10521; Sigma-Aldrich) and placed on a wet sponge. Using straight fine forceps (Cat#11412-11; Fine Science Tools), approximately 0.5 mm from the proximal region of the caudal fin was gently compressed horizontally, causing physical damage to the caudal peripheral nerve [9]. Then two groups of Tg(MBP:eGFP) male zebrafish (8 months old) were incubated in plastic tanks containing 150 mL water with or without fascaplysin (final concentration 100 nM) for 10 days at 28°C, changing the water every 3 days. The fish were fed regular food twice daily (10 mg/fish/meal) throughout the experiment. The fluorescence of MBP-eGFP was examined using an INTENSILIGHT C-HGFI Illuminator (Nikon) with a GFP filter.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software). For multiple comparisons, one-way ANOVA followed by Bonferroni's post hoc test was applied if the F value reached $P<0.05$ and variance homogeneity was not violated. Student's *t*-test was used for comparisons between two groups, and Tukey's multiple comparisons test was performed to detect any significant differences between group means ($P<0.05$). In all analyses, $P<0.05$ was taken to indicate statistical significance. Data are presented as the mean±SD. The group size for *in vivo* experiments was $n\geq3$, which was recognized as the minimum sample size required to detect a prespecified effect size.

Results

Dose-dependent effects of fascaplysin in zebrafish embryos and adults

As shown in Fig. 1, fascaplysin treatment showed dose-dependent effects in both zebrafish embryos and adults. In zebrafish embryos, fascaplysin treatment affected survival, hatching rate, and heart rate in a dose-dependent manner. At a concentration of 100 μM, survival dropped to 0% within 12 hours. At 10 μM, survival reached 0% by 96 hours, and at 1 μM, it declined to 0% by 120 hours. By contrast, embryos exposed to lower concentrations (100 nM and 10 nM) maintained 100% survival throughout the 120-hour observation period (Fig. 1A).

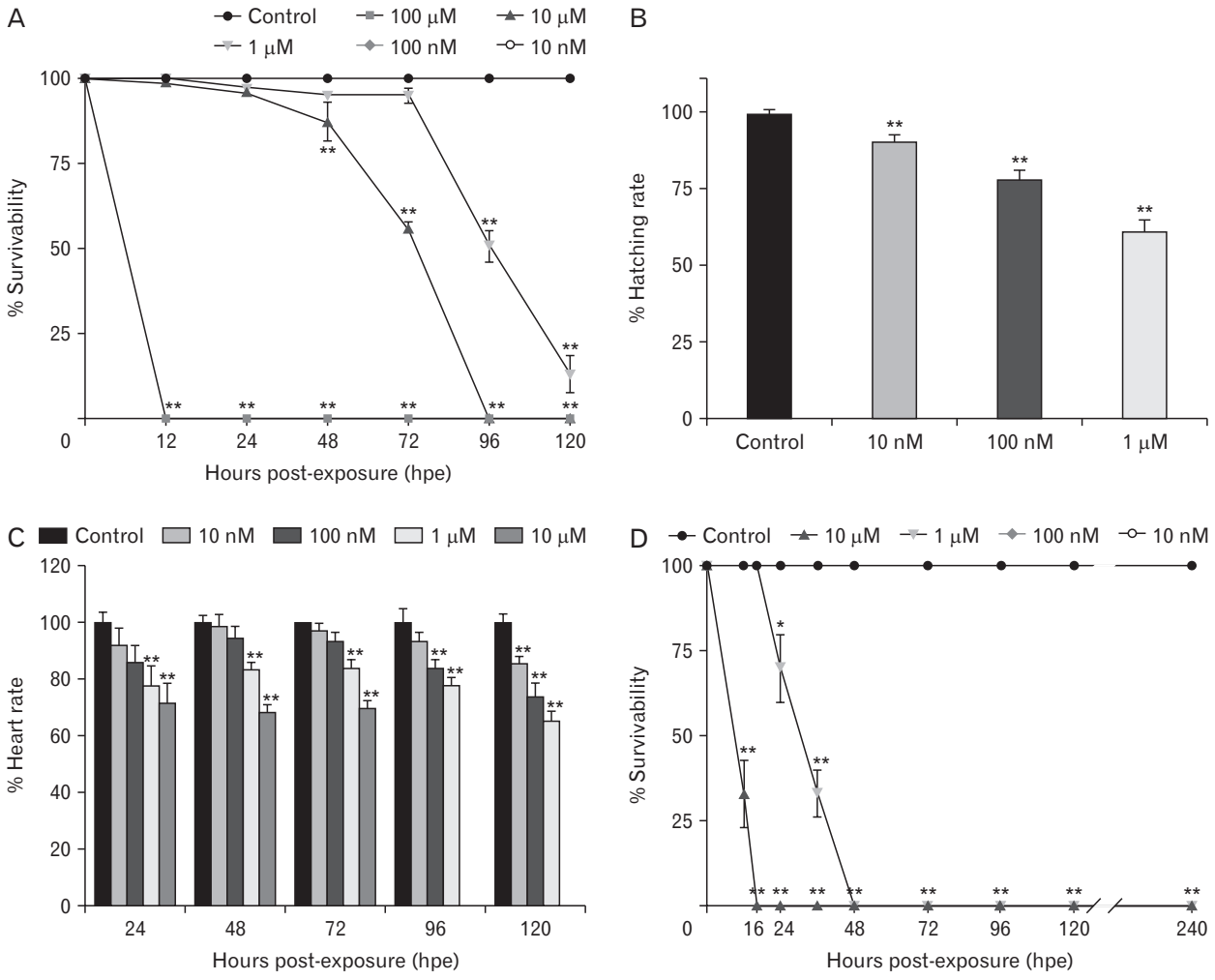

Fig. 1. Effects of fascaplysin on survival, hatching, and heart rate in zebrafish. (A) Survival rates of zebrafish embryos from 12 to 120 hours post-exposure (hpe) to fascaplysin. (B) Hatching rates of zebrafish embryos at 96 hpe. (C) Heart rates of zebrafish embryos from 24 to 120 hpe. (D) Survival rates of adult zebrafish from 0 to 240 hpe following exposure to fascaplysin. Data are presented as the mean±SD of triplicate experiments. Survival rates from Significant differences from the untreated control group are indicated by **P*<0.05, ***P*<0.01.

Hatching began at 48 hours in all groups, with the majority of embryos hatching by 96 hours. However, at 1 μM fascaplysin, the hatching rate was significantly reduced, reaching only 60% by 96 hours. Embryos exposed to 10 nM and 100 nM fascaplysin also showed a significant decrease in hatching rate compared to controls (Fig. 1B). There was also a dose-dependent reduction in heart rate following fascaplysin exposure, with higher concentrations resulting in a greater decrease relative to controls (Fig. 1C).

In adult zebrafish, exposure to 10 μM fascaplysin resulted in 100% mortality within 16 hours post-exposure (hpe), while 1 μM exposure caused complete mortality by 48 hpe. By contrast, adult zebrafish exposed to 100 nM and 10 nM showed no adverse effects even after more than 10 days of continuous exposure (Fig. 1D). Based on these findings, 100 nM was selected as the optimal concentration for subsequent chronic exposure experiments to ensure both efficacy and safety.

These results collectively highlight the concentration-dependent toxicity of fascaplysin in zebrafish at different developmental stages, providing a basis for selecting appropriate experimental conditions.

Effects of fascaplysin on melanocyte formation in zebrafish embryos

As shown in Fig. 2, fascaplysin exposure affected melanocyte formation in a dose-dependent manner. Representative images captured 24 hours after treatment (Fig. 2A) illus-

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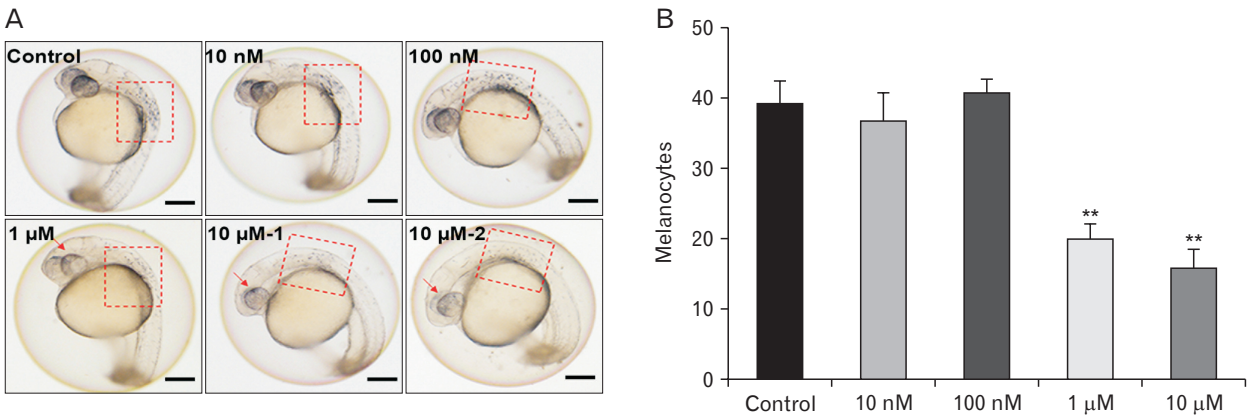

Fig. 2. Effects of fascaplysin on melanocyte development in zebrafish embryos. (A) Representative images of melanocyte development in zebrafish embryos exposed to the indicated concentrations of fascaplysin, captured at 24 hours post-exposure. The red arrow indicates a change in eye color. Scale bar=0.1 mm. (B) Melanocyte counts within the designated red square areas shown in (A). Three embryos per group were analyzed in three independent experiments, and data are presented as the mean±SD. Significant differences compared to the untreated control group are indicated by $^{**}P<0.01$.

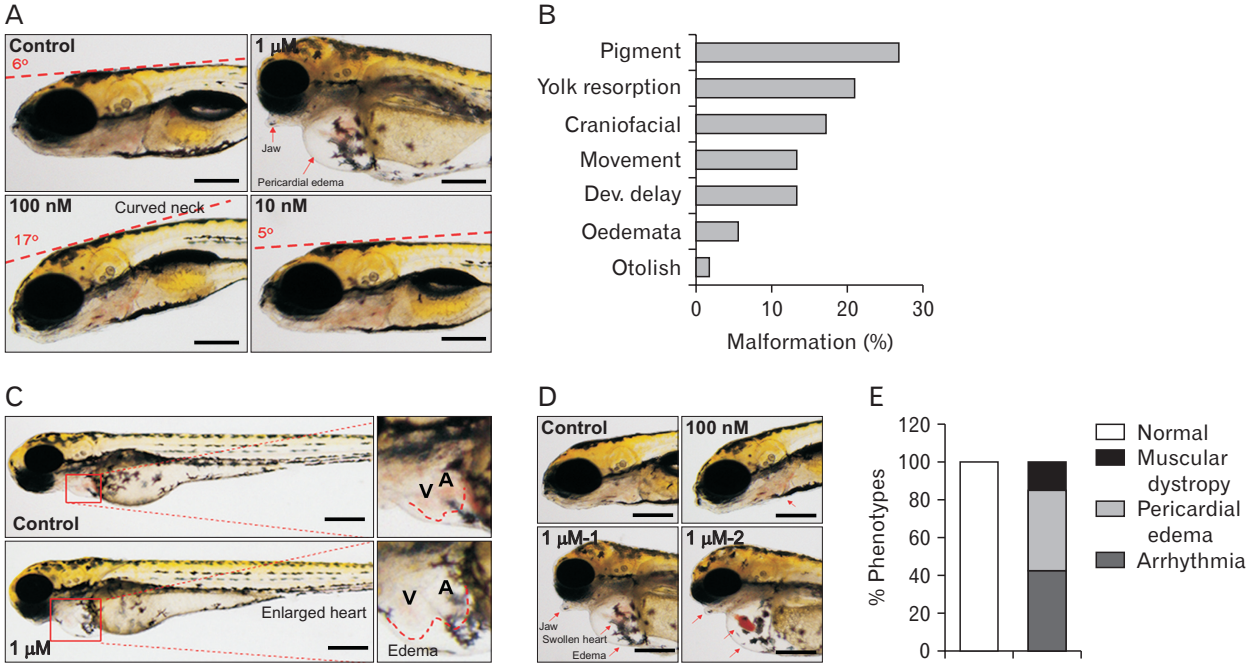

Fig. 3. Morphological and cardiac effects of fascaplysin exposure in zebrafish larvae. (A) Representative images of zebrafish larvae at 96 hours post-exposure (hpe) to 10 nM, 100 nM, and 1 μM. Larvae exposed to 1 μM fascaplysin showed pericardial edema and jaw malformation (red arrow). Scale bar=0.1 mm. (B) Incidence of various morphological malformations in zebrafish larvae at 120 hpe to 1 μM fascaplysin. (C) Lateral view of zebrafish larvae at 72 hpe to 1 μM fascaplysin. While control larvae (0.03% DMSO) exhibited normal cardiac morphology, fascaplysin (1 μM)-exposed larvae showed pericardial edema and enlargement of both the atrium "A" and ventricle "V". Scale bar=0.1 mm. (D) Zebrafish larvae with long-term (120 hours) exposure to 1 μM fascaplysin showed severe cardiac malformations, including venous congestion and enlargement of the heart (red arrows). Scale bar=0.1 mm. (E) Quantification of muscular dystrophy, pericardial edema, and arrhythmia in zebrafish larvae exposed to 1 μM fascaplysin for 120 hours based on three independent experiments (n=30 zebrafish/group). Dev., developmental.

trated changes in the presence of melanocytes corresponding to fascaplysin concentration. Quantitative analysis (Fig. 2B) showed no significant differences in melanocyte count at lower concentrations (10 nM and 100 nM) compared to controls. However, at higher concentrations (1 μM and 10 μM), there was a marked reduction in melanocyte count, with de-

creases exceeding 50% relative to the control. These findings indicate that fascaplysin concentrations of 1 μM or higher significantly inhibited melanocyte formation in zebrafish embryos.

Morphological and functional abnormalities induced by fascaplysin in zebrafish embryos

As shown in Fig. 3, fascaplysin treatment induced various morphological and functional abnormalities, affecting both peripheral and abdominal structures and causing notable cardiac effects. The observed deformities included hemorrhage (blood pooling outside the circulation), abnormal body shape (such as scoliosis, bent tail, and detached tail), enlarged yolk sac, disrupted pigmentation, and reduced motility. Pericardial edema and jaw malformation were apparent in embryos at 96 hpe to 1 μM fascaplysin (Fig. 3A), while 100 nM fascaplysin led to abnormal neck morphology. In addition, embryos treated with 1 μM fascaplysin showed depigmentation and impaired movement (dyskinesia) by 120 hpe (Fig. 3B).

Cardiac abnormalities were particularly prominent. By 72 hpe, fascaplysin-treated zebrafish exhibited enlargement of the hearts and venous congestion (Fig. 3C), progressing to blood pooling and clotting within the heart chambers and reduced circulation by 120 hpe. Both atrial and ventricular swelling, accompanied by fluid accumulation around the heart, suggested significant edema (Fig. 3D). Cardiac contractility was notably reduced, and ventricular area enlargement was observed (Fig. 3E). These findings indicate that a high concentration of fascaplysin had broad toxic effects on the organs of developing zebrafish, with marked impacts on cardiac morphology and function.

Inhibitory effects of fascaplysin on oxidative stress markers in adult zebrafish treated with ethanol

In ethanol-exposed adult zebrafish, RT-qPCR analysis showed that fascaplysin (100 nM) significantly reduced expression levels of genes associated with superoxide produc-

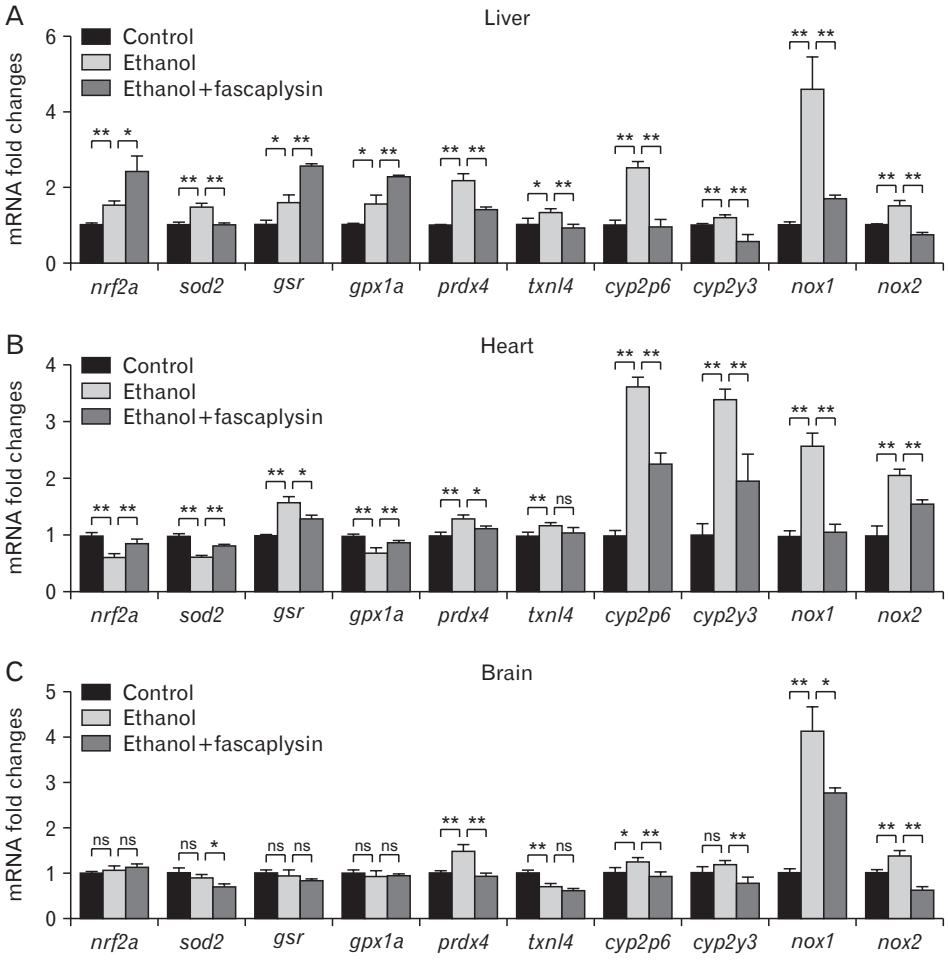

Fig. 4. Effects of fascaplysin on alcohol-induced oxidative response dysfunction in adult male zebrafish. Relative mRNA expression of genes associated with oxidative stress in (A) liver, (B) heart, and (C) brain tissues. The genes *nrf2a*, *sod2*, *gsr*, *gpx1a*, *prdx4*, and *txnl4* were analyzed as markers of oxidative stress responses, while *cyp2y3*, *cyp2p6*, *nox1*, and *nox2* served as markers for superoxide production. Data are presented as the mean±SD. **P*<0.05, ***P*<0.01. ns, not significant.

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tion, including *cyp2y3*, *cyp2p6*, *nox1*, and *nox2*, across the liver, heart, and brain tissues (Fig. 4). By contrast, changes in the expression of genes involved in the general oxidative stress response, such as *nrf2a*, *sod2*, *gsr*, *gpx1a*, *prdx4*, and *txnl4*, were less marked. These results indicate that fascaplysin specifically targets pathways related to superoxide generation rather than broadly modulating the oxidative stress response, suggesting a focused role in reducing oxidative damage within ethanol-exposed tissues, particularly where superoxide-mediated pathways are critical.

Protective effects of fascaplysin on peripheral nerve injury in transgenic zebrafish

Morphometric analysis using transgenic Tg(MBP:eGFP) zebrafish expressing eGFP in Schwann cells, demonstrated the protective effects of fascaplysin on peripheral nerve integrity following localized injury (Fig. 5A). In both embryonic and adult zebrafish, GFP fluorescence labeled the Schwann cells within the caudal fin, a nonmuscular appendage supported by 16 to 18 principal bony rays and surrounded by mesenchymal tissue containing peripheral nerves. After inducing localized nerve injury in the caudal fin, GFP fluorescence gradually decreased in the DMSO-treated control group by 10 days postinjury. By contrast, treatment with 100 nM fascaplysin effectively preserved GFP fluorescence, indicating protection of Schwann cells and peripheral nerves in the zebrafish tail fin (Fig. 5B, C). In the DMSO-treated control group, GFP-positive nerves were nearly undetectable by 7 days postinjury. However, the fascaplysin-treated group maintained visible fluorescence even at 10 days postinjury (Fig. 5C, D). These observations suggest a potential role of fascaplysin in preventing peripheral nerve degeneration after injury, possibly by stabilizing Schwann cell structure and function in injured nerve areas.

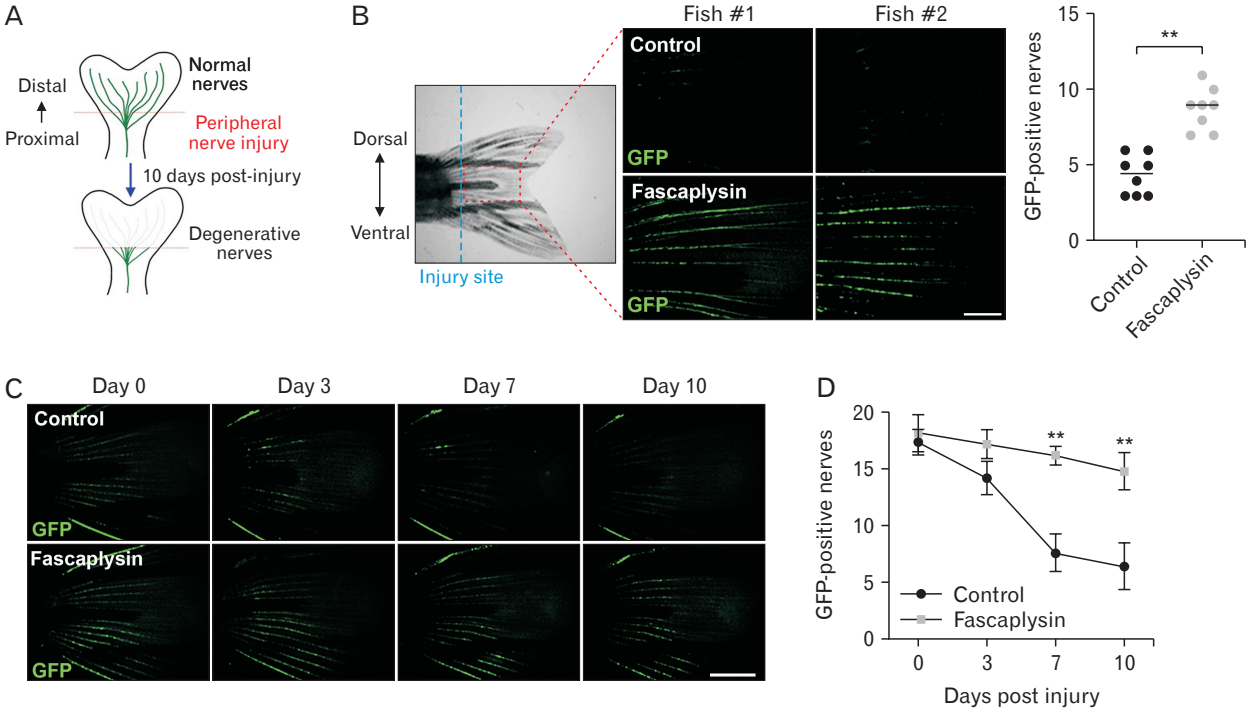

Fig. 5. Inhibitory effects of fascaplysin on in vivo zebrafish peripheral nerve degeneration (PND) in a zebrafish model. (A) Schematic representation of the *in vivo* PND model in transgenic adult zebrafish (Tg[MBP:eGFP]). Zebrafish were exposed to 100 nM fascaplysin for 10 days at 28.5°C following induction of PND. (B) Fluorescence image (green, MBP) of the zebrafish caudal fin obtained after 10 days of fascaplysin treatment captured with a fluorescence stereomicroscope. The count of fluorescence-positive nerves in the caudal fin is shown in the right panel. $^{**}P<0.01$ compared to control. Scale bar=2 mm. (C) Fluorescence images of the zebrafish caudal fin were obtained after 0, 3, 7, and 10 days of fascaplysin treatment. Scale bar=2 mm. (D) Quantification of GFP-positive nerve fibers in the caudal fin at each time point, presented as the mean±SD from three independent zebrafish. $^{**}P<0.01$. MBP, myelin basic protein; GFP, green fluorescent protein; eGFP, enhanced green fluorescent protein.

Discussion

The present study investigated the peripheral neuroprotective potential and toxicological profile of fascaplysin using zebrafish models. Fascaplysin exhibited concentration-dependent effects on embryonic development, oxidative stress marker expression, and peripheral nerve integrity. These results extend the understanding of the biological activities of fascaplysin, particularly in the context of peripheral nerve protection, and are consistent with previous reports regarding its multifaceted pharmacological properties.

At higher concentrations (≥1 μM), fascaplysin showed pronounced toxicity in zebrafish, as evidenced by decreased survival rates (Fig. 1A, D), delayed hatching (Fig. 1B), impaired cardiac function (Fig. 1C), and morphological abnormalities (Fig. 3). Similar toxic effects have been reported in other studies, where fascaplysin was shown to induce apoptosis and cell cycle arrest in cancer cell lines due to strong inhibition of CDK4 and DNA intercalation [14, 15]. The observed cardiotoxic effects may be attributable to interference with critical signaling pathways involved in cardiac development and function. For example, CDK4 inhibitors have been shown to affect cardiac myocytes, leading to decreased proliferation and potential developmental defects [16].

The inhibition of melanocyte formation at higher concentrations (Fig. 2) was consistent with previous reports on the effects of fascaplysin on pigment cells [17]. Melanocytes originate from neural crest cells, which also give rise to Schwann cells [18]. Therefore, the observed disruption of melanocyte development suggests that fascaplysin may also affect other neural crest derivatives, including Schwann cells. Neural crest cells share common signaling pathways during differentiation, such as the Wnt and Notch pathways [19], suggesting that the impact of fascaplysin on melanocyte formation might extend to Schwann cell development and function. The reduction in melanocyte count suggests that fascaplysin may disrupt melanocyte differentiation or survival, possibly through inhibition of tyrosinase activity, which is essential for melanin synthesis [20].

The experiments on adult zebrafish provided compelling evidence for the neuroprotective effects of fascaplysin on peripheral nerves. The reduction in expression of superoxide-producing enzymes (*cyp2y3*, *cyp2p6*, *nox1*, and *nox2*) suggested that fascaplysin mitigates oxidative stress, which contributes to peripheral nerve damage (Fig. 4). Previous research has highlighted the role of oxidative stress in the pathogenesis of peripheral neuropathies, such as diabetic neuropathy, and the potential of antioxidants for ameliorating nerve damage [21, 22]. The ability of fascaplysin to reduce oxidative stress is consistent with previous observations that marine-derived compounds possess significant antioxidant properties [23].

The preservation of Schwann cells and peripheral nerve integrity in fascaplysin-treated zebrafish following injury was particularly noteworthy (Fig. 5). Schwann cells are critical for myelination and nerve regeneration in the PNS. Promotion of Schwann cell survival and function enhances nerve repair processes [5, 24]. The neuroprotective effect of fascaplysin may be attributable to modulation of signaling pathways involved in cell survival and apoptosis, such as the PI3K/Akt pathway, which plays a crucial role in Schwann cell biology [25].

Other compounds have been investigated for their neuroprotective effects in peripheral nerve injury models. Curcumin, a natural polyphenol, has demonstrated antioxidant and anti-inflammatory properties that protect against peripheral nerve damage in rodent models [26]. Similarly, resveratrol has been shown to promote nerve regeneration and functional recovery after sciatic nerve injury [27]. The neuroprotective effects of fascaplysin observed in the zebrafish model in the present study add to the growing list of natural compounds with potential therapeutic benefits for peripheral neuropathies.

The specific action of fascaplysin on superoxide production pathways, rather than broadly suppressing the entire oxidative stress response, may offer advantages in minimizing side effects associated with general antioxidant therapy. Oversuppression of reactive oxygen species (ROS) can disrupt normal cellular signaling and immune responses [28]. Targeting specific oxidative pathways could provide therapeutic benefits while maintaining physiological ROS levels necessary for cellular functions.

However, the potential cardiotoxicity of fascaplysin at higher concentrations raises concerns for clinical application. Cardiotoxic effects have been a significant obstacle to the development of anticancer drugs, such as doxorubicin, which can cause dose-dependent cardiomyopathy [29]. Strategies to mitigate cardiotoxicity include the use of drug delivery systems that target specific tissues, thus reducing systemic exposure [30]. Applying similar approaches to fascaplysin could enhance the therapeutic index.

Further research is needed to elucidate the molecular

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mechanisms underlying the neuroprotective effects of fascaplysin. Investigating the impact of fascaplysin on signaling pathways involved in Schwann cell survival, such as the ERK1/2 and JNK pathways, could provide insights into its mode of action [31].

The use of zebrafish models offers advantages for high-throughput screening and real-time observation of developmental processes. However, translating findings from zebrafish to human physiology requires careful consideration due to species-specific differences. Validation of the neuroprotective effects of fascaplysin in mammalian models of peripheral nerve injury, such as rodent sciatic nerve crush or transection models, would strengthen the case for its therapeutic potential [32].

In clinical contexts, peripheral neuropathies remain challenging to treat, with current therapies focusing primarily on pain management and symptomatic relief [33]. The development of disease-modifying treatments that promote nerve repair is a significant unmet need. Natural compounds such as fascaplysin offer a promising avenue due to diverse biological activities and potential for multitarget effects [34].

In conclusion, fascaplysin exhibits neuroprotective effects on peripheral nerves at low concentrations, with the ability to reduce oxidative stress and preserve Schwann cell integrity following injury. These findings contribute to the understanding of fascaplysin as a potential therapeutic agent for peripheral neuropathies. Future studies should focus on elucidating the molecular mechanisms involved, optimizing dosing strategies to minimize toxicity, and validating efficacy in mammalian models. The integration of fascaplysin into therapeutic strategies could offer new hope for treatment of peripheral nerve injuries and neuropathies.

ORCID

Ki-Hoon Park: https://orcid.org/0009-0001-5818-758X
Youngbuhm Huh: https://orcid.org/0000-0002-7687-0374
Hyung-Joo Chung: https://orcid.org/0000-0001-9545-3245
Hiroyuki Konishi: https://orcid.org/0000-0002-4321-8339
Junyang Jung: https://orcid.org/0000-0003-3946-5406
Na Young Jeong: https://orcid.org/0000-0003-2130-4719

Author Contributions

Conceptualization: KHP, NYJ, JJ. Data acquisition: KHP. Data analysis or interpretation: KHP, YH, HJC, HK, JJ, NYJ. Drafting of the manuscript: KHP. Funding acquisition: KHP, HJC, JJ, NYJ. Critical revision of the manuscript: JJ, NYJ. Approval of the final version of the manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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