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Anti-aging effects of active medicinal-food homologous complex nutrients in zebrafish

Yinan Yuan[1,2*], Fuqiao Xu[2], Hanluo Li[3], Sini Kang[3], Yiming Wen[3], Heng Liu[2], Xiaoze Ren[2], Lan Yuan[1,2]

[1]Davinature Precision Nutrition Academy Limited, Auckland 2013, New Zealand; [2]Hangzhou Ruilin Food Technology Co., Ltd. Hangzhou City 311599, Zhejiang Province, China; [3]National "111" Center for Cellular Regulation and Molecular Pharmaceutics, Wuhan Joint Laboratory (China-Serbia) of Biomedical and Health Science, School of Life and Health Sciences, Hubei University of Technology, Wuhan, 430068, China

***Corresponding Author:** Yinan Yuan, PhD, Davinature Precision Nutrition Academy Limited 72 Matarangi Road, Auckland 2013, New Zealand. Email: eninan88@hotmail.com

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ABSTRACT

Background: Aging is a complex biological process characterized by progressive cellular and molecular deterioration, including oxidative stress accumulation, telomere attrition, and cellular senescence. Active medicinal–food homologous complex nutrients (AMCN) are bioactive compounds derived from natural sources with potential anti-aging effects, but their mechanisms remain poorly understood.

Objective: To investigate the anti-aging effects of AMCN and their underlying molecular mechanisms using a zebrafish aging model.

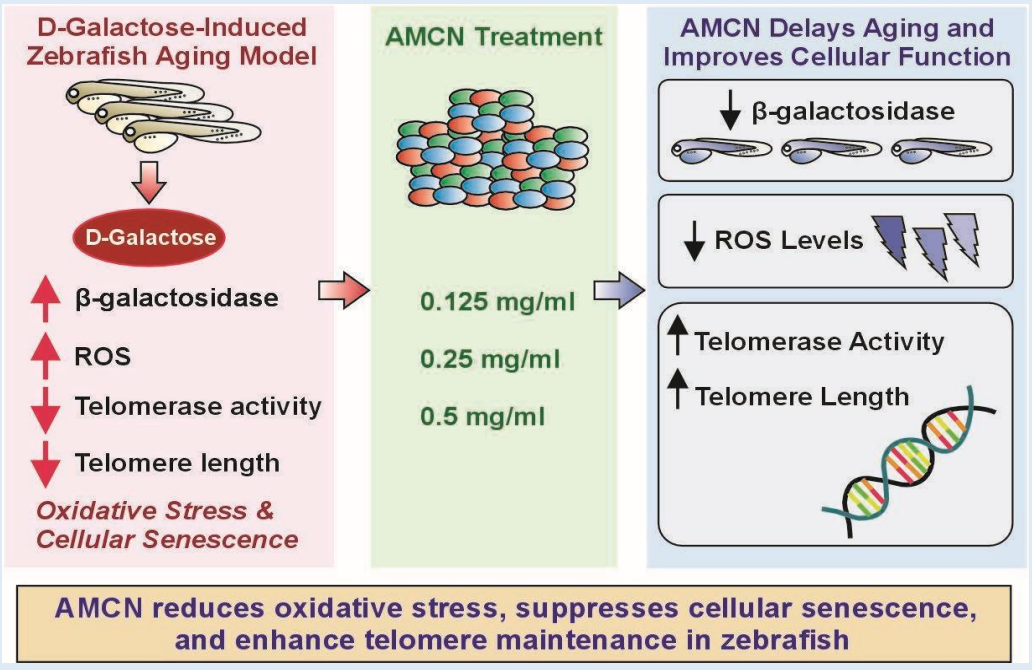
Methods: Zebrafish were subjected to an aging model and treated with varying concentrations of AMCN. Aging biomarkers were assessed, including β-galactosidase activity, intracellular reactive oxygen species (ROS), telomerase protein concentration, and telomere length.

Results: AMCN treatment significantly decreased β-galactosidase staining intensity as well as ROS levels in a dose-dependent manner. Telomerase protein concentration was elevated, and telomere length was partially restored, particularly at moderate and higher AMCN concentrations.

Novelty of Study: This study demonstrates, for the first time in a whole-organism vertebrate model, that active medicinal–food homologous complex nutrients (AMCN) exert coordinated, multi-target anti-aging effects in a zebrafish model by reducing oxidative stress, attenuating cellular senescence, and preserving telomere integrity. By establishing a functional association between redox regulation and telomere maintenance, this study provides mechanistic evidence supporting the role of AMCN in modulating key processes involved in aging. The use of zebrafish as a translational vertebrate model enables in vivo evaluation of these effects and enhances the physiological relevance of AMCN, supporting their application in the development of nutraceuticals and functional foods aimed at mitigating age-related decline and maintaining physiological homeostasis. These findings highlight AMCN as a promising multi-component dietary intervention targeting interconnected hallmarks of aging.

Conclusions: AMCN exerts protective effects against aging-related cellular dysfunction by reducing oxidative stress, suppressing senescence, and maintaining telomere stability. These results provide scientific support for the potential use of AMCN as a functional dietary intervention to promote healthy aging and prevent age-related functional decline.

Keywords: Active medicinal–food homologous complex nutrients, functional food, zebrafish model, anti-aging, reactive oxygen species, telomerase, telomere, oxidative stress , cellular senescence



Graphical Abstract: Anti-aging effects of AMCN in a zebrafish aging model.

INTRODUCTION

Aging is a complex, multifactorial biological process characterized by the gradual decline of physiological function and increased susceptibility to disease over time. Rather than arising from a single cause, aging results from the progressive accumulation of molecular and cellular damage that affects nearly all tissues and organ systems [1]. At the cellular level, aging is associated with a set of conserved biological features known as the hallmarks of aging, which include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication [1]. Together, these changes impair tissue homeostasis, reduce regenerative capacity, and contribute to functional deterioration and increased mortality risk [2]. Among these hallmarks, oxidative stress and telomere dysfunction play particularly important roles in driving aging. Excessive production of reactive oxygen species (ROS) promotes DNA damage, protein oxidation, lipid peroxidation, and mitochondrial impairment, thereby accelerating cellular dysfunction and senescence [2, 3]. Telomeres, which protect chromosome ends, progressively shorten with cell division and are highly sensitive to oxidative damage; excessive telomere erosion can trigger cellular senescence or apoptosis and promote tissue degeneration [4]. In contrast, telomerase activity can partially preserve telomere length and delay aging-related decline [5]. In parallel, disruption of protein homeostasis, mitochondrial dysfunction, and stem cell exhaustion further exacerbate aging by limiting cellular repair, energy production, and tissue regeneration [1,6]. However, most existing studies have examined these mechainsms independently, and the interactions between oxidative stress regulation and telomere maintenance remain insufficiently characterized in the context of complex nutritional interventions. Collectively, these mechanisms highlight aging as a dynamic and modifiable process, providing a biological basis for interventions aimed at promoting healthy aging and extending life span.

Active medicinal–food homologous complex nutrients (AMCN) are derived from natural materials traditionally classified under the concept of “medicine–food homology,” which recognizes certain foods as having both nutritional and therapeutic functions [6]. In traditional Chinese medicine and related dietary systems, these materials have long been consumed to promote health maintenance, delay functional decline, and prevent age-associated disorders [7]. AMCN formulations typically combine multiple bioactive components, including polysaccharides, flavonoids, glycoproteins, and phenolic compounds, which exert complementary biological effects such as antioxidant activity, regulation of metabolism, modulation of cellular stress responses, and preservation of cellular homeostasis [8]. Advances in processing strategies such as fermentation and biotransformation have been shown to enhance the bioavailability and biological efficacy of AMCN by converting high–molecular weight or poorly absorbed compounds into more readily absorbable metabolites [6]. Although these bioactive nutrients have been reported to modulate oxidative stress and inflammation [9], existing studies predominantly focus on individual bioactivities, and the mechanisms by which AMCN coordinately regulate multiple hallmarks of aging—particularly the interplay between redox balance, cellular senescence, and telomere maintenance remain largely unclear.

Zebrafish have emerged as a valuable vertebrate model for aging research due to their genetic similarity to humans, well-characterized lifespan, and suitability for both genetic and pharmacological manipulation. Importantly, zebrafish exhibit many conserved features of human aging, including progressive decline in cognitive and motor function, accumulation of lipofuscin, increased oxidative stress, telomere shortening, mitochondrial dysfunction, and reduced regenerative capacity with age [10, 11]. Aging and accelerated-aging

models in zebrafish, induced by oxidative stressors or chemical agents, recapitulate key molecular and cellular hallmarks observed in mammalian aging, such as DNA damage, cellular senescence, and tissue degeneration [12]. In addition, the transparency of zebrafish during early life stages and their responsiveness to dietary and environmental interventions make them suitable for evaluating anti-aging effects of functional foods and bioactive compounds [13, 14]. In this study, we employed a zebrafish aging model to systematically investigate the multi-target anti-aging mechanisms of AMCN by simultaneously evaluating key aging-related biomarkers, including ROS levels, β-galactosidase activity, telomerase activity, and telomere length. This integrative approach enables the elucidation of coordinated interactions among oxidative stress, cellular senescence, and telomere dynamics, thereby addressing a critical gap in current aging research and strengthening the mechanistic basis for AMCN as a functional nutritional intervention.

MATERIALS AND METHODS

AMCN Synthesis: AMCN was produced as described in our previous study (6). Briefly, single-clone Ganoderma lucidum was first cultured in liquid medium under controlled conditions to generate a β-glucosidase–enriched supernatant. Once enzymatic activity exceeded 100 mU/mL, the culture was centrifuged and the supernatant was collected. Powders of Polygonatum, Ganoderma lucidum, and mulberry leaves were then added to the supernatant and incubated to allow enzymatic biotransformation of macromolecular constituents into more bioavailable forms. After biotransformation, the mixture was further fermented with Lactobacillus plantarum to enhance bioactivity and stability, producing the AMCN. The fermented supernatant was subsequently supplemented with lyophilization protectants, freeze-dried, and milled to obtain a homogeneous powder, which was stored under dry, light-protected conditions as the final AMCN product.

Zebrafish husbandry and embryo collection: Zebrafish were maintained and bred as described in our previous study (13). Briefly, all zebrafish procedures were conducted in accordance with approval from the Institutional Animal Care and Use Committee (MDL2025-03-04-03). Adult zebrafish were maintained in a recirculating aquaculture system (Hunter Biotech, Hangzhou, China) at a constant temperature of 28 °C with a photoperiod of 14 h light and 10 h darkness, and were fed three times per day. For embryo collection, male and female fish were placed together at a 1:1 ratio in the evening with a physical divider. The divider was removed the next morning, permitting spawning within the first hour after lights-on. Fertilized embryos were then collected and placed in 10-cm Petri dishes containing 1× E3 medium supplemented with 0.3 ppm methylene blue, and incubated at 28.5 °C in a controlled environmental incubator (BluePard, Yiheng Scientific Instrument, Shanghai, China) under the same light–dark conditions until experimental treatment.

Groups and treatment: Six experimental groups were included: (1) normal control, (2) model, (3) positive control (treated with 0.02 mg/mL resveratrol), and (4) three AMCN treatment groups (0.125, 0.25, and 0.5 mg/mL of AMCN, respectively). At 6 hours post-fertilization (hpf), zebrafish embryos were selected and cultured in six-well plates at a density of 30 embryos per well. The normal control group was maintained under standard culture conditions. The model control group, positive control group, and treatment groups were exposed to 40 mg/mL D(+)-Galactose (CAS No.: 59-23-4; Lot No.: D274314; Shanghai Aladdin Biochemical Technology Co., Ltd., Shanghai, China) to induce aging-related oxidative stress. Concurrently, the positive control group received 20 μg/mL resveratrol in addition

to D(+)-Galactose exposure, while the treatment groups received the test samples at the specified concentrations together with D(+)-Galactose. All AMCN treatments were conducted at 28 °C for 48 hours.

β-galactosidase staining: At 72 hpf, 10 zebrafish larvae from each experimental group were randomly chosen and placed into 1.5 mL microcentrifuge tubes. The larvae were washed three times with 1× PBS, with each wash lasting 5 minutes, and subsequently fixed in 4% paraformaldehyde (PFA) at 4 °C overnight. Following fixation, the PFA was removed. A β-galactosidase staining solution (Baihuan Biotechnology, Guangzhou, China) was freshly prepared according to the manufacturer's protocol and added to each tube. The samples were then incubated at 37 °C overnight in the dark. On the following day, the staining solution was discarded, and the larvae were washed with PBS. Images were acquired, and β-galactosidase staining intensity was quantified using ImageJ software.

Assessment of ROS levels: After 72 hours of treatment, 10 zebrafish larvae were randomly selected from each experimental group and stained with CellROX™ Green Reagent (M10424; Nanjing Wobo Biotechnology Co., Ltd., Nanjing, China) as a probe for oxidative stress detection. Fluorescence images were captured using a fluorescence microscope, and RO fluorescence intensity was quantified to evaluate the anti-aging activity of AMCN-FD. Fluorescence images were obtained using a ZEISS Axio Zoom V16 fluorescence microscope (Germany). The fluorescence intensity was subsequently quantified using ImageJ software.

Assessment of telomerase levels: At 72 hpf, 10 zebrafish larvae from each experimental group were collected and processed for analysis. The samples were placed into 1.5 mL microcentrifuge tubes, and physiological saline was added at a ratio of 1:9 (weight/volume). The tissues were homogenized on ice and subsequently centrifuged at 5,000 × g for 10 min at 4 °C. The resulting supernatant was used to determine telomerase levels using a commercial ELISA kit (BI00152FB, Baihuan Biotechnology Co., Ltd., Guangzhou, China) in accordance with the manufacturer's protocol. Telomerase protein levels were normalized to total protein content and expressed as ng per mg protein.

Detection of telomere length: At 72 hpf, 10 zebrafish larvae were collected from each experimental group following daily renewal of the culture medium. Thirty larvae per group were homogenized and genomic DNA was isolated using a commercial DNA extraction kit (Qiagen, USA). Telomere length was assessed by quantitative real-time PCR using a fluorescence PCR system (LongGene Q2008, Hangzhou, China). The amplification protocol consisted of an initial denaturation step at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s and annealing/extension at 54 °C for 2 min. Relative telomere length was determined by quantitative PCR and expressed as the telomere-to-single-copy gene ratio, using c-fos as the reference gene. Primer sequences used for telomere and reference gene amplification are provided in Table 1.

Statistical Analyses: Statistical analysis was performed using one-way ANOVA followed by Dunnett's post hoc test to compare the normal control and AMCN treatment groups against the model group. All quantitative data are presented as mean ± standard error of the mean (SEM). Analyses were conducted using GraphPad Prism software (version 8.0.2, GraphPad Software Inc., CA, USA) in a blinded manner. A p-value < 0.05 was considered statistically significant.

Table 1. The sequence of primers used in qPCR

Primer	Sequence (5' to 3')
z-q-Tel-F	GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT
z-q-Tel-R	TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA
z-q-c-fos-F	CAGCTCCACCACAGTGAAGA
z-q-c-fos-R	GCTCCAGGTCAGTGTTAGCC

RESULTS AND DISCUSSION

AMCN reduced β-galactosidase levels in zebrafish: β-galactosidase staining was used to assess cellular senescence, as its activity increases with age and it is a widely established marker of senescent cells in zebrafish (15). We showed that β-galactosidase staining intensity in the zebrafish aging model group was significantly higher compared to the normal control, indicating that the establishment of our model was successful (Fig. 1A&B). Notably, AMCN treatment in the model resulted in a significant decrease in β-galactosidase staining compared with the non-treated model group, even at the lowest concentration tested (Fig. 1B). However, the AMCN treatment groups did not show an apparent dose-dependent decrease in β-galactosidase staining intensity.

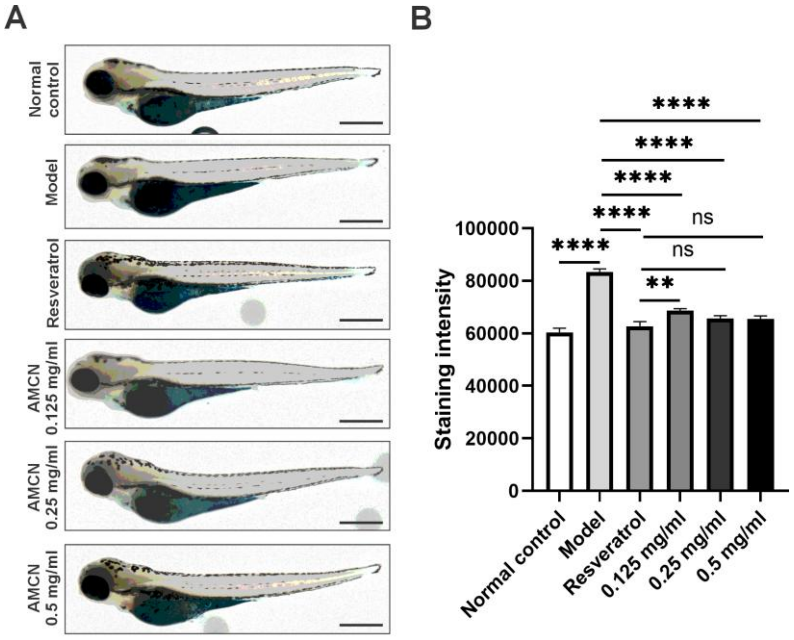


Figure 1. Effect of AMCN on β-galactosidase activity in a zebrafish aging model. (A) Representative images of zebrafish larvae from each study group following β-galactosidase staining. Scale bar = 0.5 mm. (B) β-galactosidase staining intensity of zebrafish larvae in each study group. Data are presented as mean ± SEM (n=10/group), ns, not statistically significant, **p < 0.01, ****p < 0.0001 for comparison with the model group, or between AMCN and Resveratrol, (one-way ANOVA followed by Dunnett's post hoc test).

AMCN reduced ROS levels in zebrafish: We demonstrated that the fluorescence intensity of ROS in the zebrafish aging model was significantly higher than that in the normal control (Fig. 2A&B). Quantification showed that AMCN treatment in the model led to a significant decrease in ROS fluorescence intensity compared with the model, and the effect was dose-dependent (Fig. 2B).

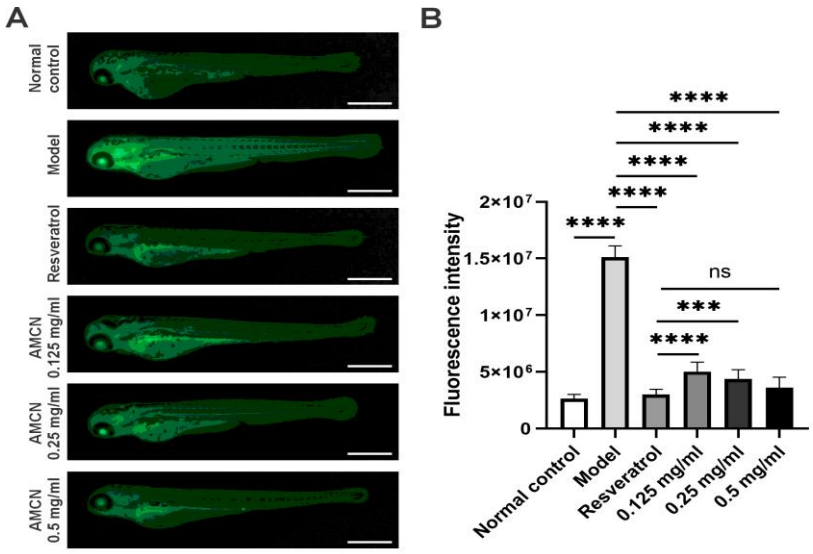


Figure 2. Effect of AMCN on ROS levels in a zebrafish aging model. (A) Representative images of zebrafish larvae from each study group. ROS was detected in zebrafish larvae with DCFH-DA fluorescent probes. Scale bar = 0.5 mm. (B) ROS fluorescence intensity of zebrafish larvae in each study group. Data are presented as mean ± SEM (n=10/group), ns, not statistically significant, ***p < 0.001, **** p < 0.0001 for comparison with the model group, or between AMCN and Resveratrlol (one-way ANOVA followed by Dunnett's post hoc test).

AMCN enhanced telomerase activity and increased telomere length in zebrafish: We used ELISA to measure telomerase protein concentration in the zebrafish model and found that it was significantly decreased in the non-treated model group compared with the normal control (Fig. 3A). However, AMCN treatment resulted in a significantly higher telomerase concentration compared with the non-treated model group, and this effect appeared to be dose-dependent (Fig. 3A). Consistently, the zebrafish aging model exhibited significantly shorter telomere length compared with the normal control, whereas AMCN treatment significantly increased telomere length at concentrations of 0.25 and 0.5 mg/ml, but not 0.125 mg/ml, compared with the non-treated model group (Fig. 3B).

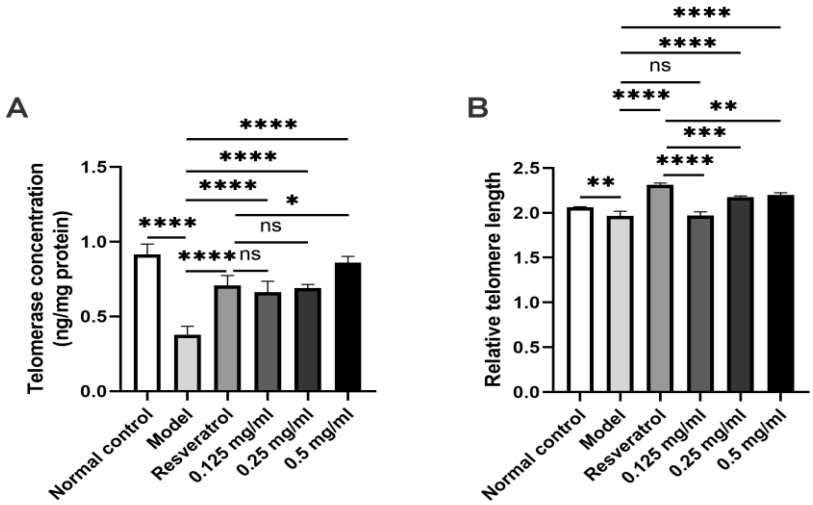


Figure 3. Effect of AMCN on telomerase concentration and telomere length in zebrafish. (A) Telomerase concentration and (B) telomere length in zebrafish larvae from each study group. Data are presented as mean ± SEM n=10 per group), ns, not statistically significant, * p < 0.05, ** p < 0.01, **** p < 0.0001 for comparison with the model group, or between AMCN and Resveratrlol (one-way ANOVA followed by Dunnett's post hoc test).

DISCUSSION: The present study demonstrates that AMCN exert protective effects against aging-related biological changes in a zebrafish model. AMCN treatment significantly reduced β-galactosidase staining intensity, decreased intracellular ROS levels, increased telomerase protein concentration, and preserved telomere length. These findings suggest that AMCN may delay aging-associated cellular dysfunction by regulating oxidative stress and maintaining genomic stability, supporting its potential application as a functional food ingredient for promoting healthy aging and aligning with key steps in functional food development, including demonstration of in vivo efficacy and mechanistic validation [15].

Cellular senescence is a major contributor to aging and age-related diseases and is characterized by irreversible growth arrest and altered cellular function [16]. Senescence-associated β-galactosidase activity is widely recognized as a reliable biomarker of cellular aging in both mammalian and zebrafish models [17]. In this study, the zebrafish aging model exhibited significantly elevated β-galactosidase staining intensity, confirming successful induction of senescence. AMCN treatment significantly reduced β-galactosidase staining intensity across all tested concentrations. AMCN treatament showed a significant reduction at 0.125 mg/mL compared with the positive control, whereas higher concentrations (0.25 and 0.5 mg/mL) showed a similar decreasing trend without reaching statistical significance. This pattern suggests that the anti-senescent activity of AMCN may not follow a strictly dose-dependent relationship. The absence of a clear dose-dependent effect suggests that AMCN may exert early or threshold-based regulatory effects on senescence-related cellular pathways. Similar observations have been reported for natural bioactive compounds, where antioxidant and cytoprotective effects can reach maximal biological responses at relatively low concentrations [18, 19].

Oxidative stress is widely recognized as a central mechanism underlying aging and chronic disease development. Excessive ROS production contributes to cellular damage through DNA oxidation, lipid peroxidation, mitochondrial dysfunction, and protein modification [20]. Functional foods rich in antioxidant phytochemicals have been shown to reduce oxidative stress and improve cellular resilience against aging-related damage [21, 22]. In the present study, ROS levels were significantly elevated in the zebrafish aging model but were markedly reduced following AMCN treatment in a dose-dependent manner. AMCN contains multiple classes of bioactive components, including polysaccharides, flavonoids, glycoproteins, and phenolic compounds, which are known to possess strong antioxidant and anti-inflammatory properties [6]. These compounds may act synergistically to scavenge ROS and enhance endogenous antioxidant defense systems, thereby contributing to improved cellular homeostasis. The comparison of AMCN with resveratrol in terms of ROS levels revealed statistically significant differences at 0.125 and 0.25 mg/mL, whereas no significant difference was observed at 0.5 mg/mL. This pattern suggests that the antioxidant effects of AMCN may approach those of resveratrol at higher concentrations, resulting in comparable ROS reduction. One possible explanation is the presence of a saturation effect, whereby ROS levels are reduced to a minimal threshold beyond which further decreases are difficult to detect. These results further support the role of AMCN as a functional food candidate with validated antioxidant activity, an essential step in establishing biological efficacy within functional food development frameworks.

Telomere shortening represents another key hallmark of aging and is closely associated with reduced cellular proliferative capacity and increased genomic instability. Telomerase plays an essential role in maintaining telomere length and supporting cellular longevity [1, 4, 5]. In this study, the zebrafish aging model exhibited reduced telomerase protein concentration and shortened telomere length, consistent with accelerated cellular aging. AMCN treatment significantly increased telomerase protein levels and partially restored telomere length, particularly at moderate and higher concentrations (0.25 and 0.5 mg/ml). These findings suggest that AMCN may support telomere maintenance mechanisms and promote cellular longevity. In addition, the effects of AMCN on telomerase activity demonstrated a distinct dose-dependent pattern, with a statistically significant difference compared to resveratrol observed only at 0.5 mg/mL, while lower concentrations (0.125 and 0.25 mg/mL) did not show significant differences. This finding suggests that the regulation of telomerase activity by AMCN may require a higher activation threshold compared to other aging-related markers such as ROS and β-galactosidase activity. Notably, although telomere length in the AMCN-treated groups remained lower than that of the resveratrol group, a clear dose-dependent increase was observed with increasing AMCN concentration. This indicates that AMCN exerts a progressive protective effect on telomere integrity, albeit with a lower potency compared to the positive control. The discrepancy between AMCN and resveratrol may be attributed to differences in their mechanisms of action, with AMCN functioning as a multi-component system that modulates multiple pathways simultaneously rather than targeting telomere regulation directly.

The relationship between telomerase activity and telomere length observed in this study provides insight into the anti-aging mechanisms of AMCN. Telomerase counteracts telomere shortening; however, telomere length is a cumulative parameter that may require sustained activation to show measurable changes [23]. Consistently, increased telomerase activity at higher AMCN concentrations was associated with significant telomere length restoration, whereas lower concentrations showed no detectable effect, suggesting a threshold-dependent response. The shorter telomere length in AMCN-treated groups compared to resveratrol further indicates that telomere regulation is influenced not only by telomerase but also by oxidative stress [23]. The concurrent reduction in ROS supports a role for AMCN in protecting telomeres from oxidative damage, a key driver of telomere attrition [24, 25].

While telomerase protein concentration was assessed using ELISA and therefore reflects expression levels rather than direct enzymatic activity, the concurrent preservation of telomere length supports the biological relevance of AMCN-mediated telomere protection. The relationship between oxidative stress and telomere attrition provides a plausible explanation for the observed protective effects of AMCN. Telomeric DNA is highly susceptible to oxidative damage due to its guanine-rich sequence, making telomeres particularly vulnerable to ROS-induced injury [4]. Therefore, the antioxidant properties of AMCN may indirectly preserve telomere integrity by reducing oxidative damage and supporting telomerase function. This integrated mechanism highlights the potential of AMCN as a multi-target functional nutrient capable of modulating several interconnected hallmarks of aging.

Zebrafish have become an increasingly valuable model for evaluating functional foods and nutraceutical compounds due to their genetic conservation with humans, rapid development, and suitability for high-throughput screening. Furthermore, zebrafish exhibit many physiological and molecular features of human aging, including oxidative stress accumulation, telomere

shortening, and reduced regenerative capacity [10, 11, 25]. The present findings further support the utility of zebrafish as a translational model for assessing dietary interventions aimed at promoting healthy aging.

Several limitations should be considered when interpreting the results of this study. First, telomerase levels were evaluated using ELISA, which measures protein expression but does not directly assess enzymatic activity. Future studies incorporating telomerase activity assays, such as the telomeric repeat amplification protocol (TRAP) [26], would provide additional mechanistic insight. Second, the specific signaling pathways through which AMCN regulates oxidative stress and telomere maintenance were not investigated. Further studies examining mitochondrial function, antioxidant enzyme systems, and inflammatory signaling pathways would help clarify the molecular mechanisms underlying AMCN activity. Additionally, long-term functional and lifespan studies are warranted to confirm the physiological benefits of AMCN supplementation.

In summary, this study demonstrates that AMCN attenuates aging-associated biological alterations in a zebrafish model by reducing oxidative stress, suppressing cellular senescence, and preserving telomere integrity. These findings provide scientific evidence supporting the potential use of medicinal–food homologous nutrients as functional dietary interventions for promoting healthy aging and preventing age-related functional decline, while contributing to the structured validation of AMCN as a functional food ingredient in accordance with contemporary functional food development frameworks [15].

CONCLUSION

In conclusion, this study demonstrates that AMCN could effectively mitigate aging-associated biological changes in a zebrafish aging model, and that AMCN promotes cellular longevity by regulating oxidative stress and supporting genomic stability. Our findings support the potential application of AMCN as a functional food ingredient to delay aging-related decline and promote healthy aging.

List of Abbreviations: AMCN: active medicinal-food homologous complex nutrients, ROS: Reactive oxygen species, hpf: hours post-fertilization. PFA: paraformaldehyde

Author's Contributions: Y., F.X., H.L., Y.W., and L.Y. conceived and designed the study. Y.Y., F.X., H.L., S.K., Y.W., and H.L. developed the methodology. Y.Y., F.X., H.L., Y.W., and H.L. conducted the investigation. X.R. acquired funding for the project. L.Y. supervised the study. Y.Y. drafted the manuscript. Y.Y., F.X., H.L., Y.W., H.L., and L.Y. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Competing Interests The authors declare no conflict of interest.

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