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Protective Effect of Soybean Peptide on Gentamicin-Induced Ototoxicity and Nephrotoxicity

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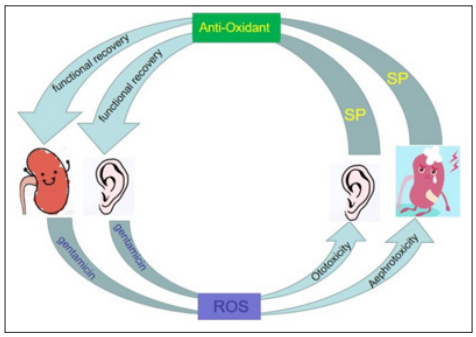
ABSTRACT

Objective: This study aimed to evaluate the effect of SP on gentamicin-induced ototoxicity and nephrotoxicity.

Methods: Brn3c:mGFP transgenic zebrafish, which have a membrane-bound green fluorescent protein (GFP) in their sensory hair cells, were administered with both gentamicin and different concentrations of SP. Moreover, C57BL/6 mice were intraperitoneally injected with gentamicin along with the intragastric administration of different concentrations of SP. After 10 days, the levels of blood urea nitrogen and serum creatinine were determined to evaluate the kidney functions in the mice. The levels of antioxidants were determined by evaluating the level of glutathione in the serum, the total antioxidant capacity, and the malondialdehyde content as well as the superoxide dismutase activity in the kidneys. Periodic Acid-Schiff staining was used to assess the lesions in the kidneys of the mice.

Results: The hair cells were observed and found to be damaged due to a decrease in gentamicin level following SP administration in the transgenic zebrafish. The kidney functions damage due to gentamicin was significantly decreased and the antioxidant levels were significantly increased after the administration of SP. The pathological characteristics of the damaged kidney tissues were partly restored by SP.

Conclusion: These findings indicate that the ototoxicity and nephrotoxicity induced by gentamicin could be repaired by SP.



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Abbreviations
SP: Soybean Peptide
BUN: Blood Urea Nitrogen
CRE: Creatinine
GSH: Glutathione
MDA: Malondialdehyde
SOD: Superoxide Dismutase
T-AOC: Total Antioxidant Capacity
ROS: Reactive Oxygen Species
CAT: Catalase
IP: Intraperitoneal Route
PAS: Periodic Acid-Schiff

Introduction

Gentamicin is an aminoglycoside antibiotic used to treat life-threatening bacterial infections such as tuberculosis, urinary or respiratory tract infections, sepsis, and suspected or confirmed neonatal bacterial infections [1,2]. It has proven most effective against bacterial strains that are resistant to other antibiotics. However, clinical studies have shown that the use of gentamicin is associated with severe ototoxicity and nephrotoxicity [3,4].

Furthermore, the use of this drug has led to hearing loss in some (20%) patients [5]. Gentamicin can accumulate in the inner ear and cause damage to the hair cells [3,6]. The ototoxicity of gentamicin is related to the excessive production of reactive oxygen species (ROS), which act on unsaturated fatty acids on the mitochondrial membrane and cause lipid peroxidation. Consequently, the mitochondrial membrane is destroyed and the apoptosis cascade is triggered, which leads to the death of the hair cells within the inner ear [7-9]. The nephrotoxicity induced by gentamicin during clinical treatment is reported to be as high as 10%–20% Gentamicin is excreted from the body via renal excretion [10]. The accumulation of gentamicin in the renal tubules could lead to epithelial cell necrosis and apoptosis and result in renal tubules dysfunction. Studies have shown that the nephrotoxicity of gentamicin is related to the induction of ROS, which leads to renal tubular necrosis, inflammation, and reduced glomerular filtration due to lipid peroxidation, protein denaturation, and DNA damage [11]. In addition, gentamicin can inhibit the production of antioxidant defense enzymes, such as superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT), which remove ROS from the kidney, resulting in an imbalance between ROS formation and antioxidant protection, thereby leading to renal cell damage [12-14].

The ototoxicity and nephrotoxicity of gentamicin are closely related the oxidative damage. At present, there is no effective treatment for the side effects of gentamicin; however, iron chelating agents, antioxidants, amino acids, hormones, and Chinese herbs have been reported to effectively reduce these effects [15-17].

Soybean peptide (SP) is an antioxidant hydrolyzed from soybean. It has high nutritional value with good solubility and is easy to digest and absorb [18]. Therefore, this study aimed to verify the protective effect of SP against the side effects of gentamicin in zebrafish and mice.

Materials and Methods

Materials

SP was provided by Sansong Biological Co., Ltd. (Shandong, China) and gentamicin was obtained from Sangon Biotech Co. Ltd. (Shanghai, China). The blood urea nitrogen (BUN), creatinine (CRE), GSH, malondialdehyde (MDA), SOD, and total antioxidant capacity (T-AOC) detection kits were purchased from Nanjing Jiancheng Bioengineering Institute Co., Ltd. (Nanjing, China).

Identification of SP

The nitrogen content was evaluated to determine the content of SP. The SP powder was dissolved into a solution (0.02 g/mL) containing 15% trichloroacetic acid (TCA). The protein content in the solution was determined using a Kjeldahl apparatus (Analytical Instrument Co., Ltd, China). An equal amount of sample was dissolved in Na2HPO4-NaH2PO4 buffer (pH, 2.2) and added into an automatic amino acid analyzer (Biochrom Group Co., LTD., UK) to determine the number of free amino acids using the external standard method. The peptide content in the sample was calculated by subtracting the number of free amino acids from the total protein content.

The molecular weight distribution of SP was determined via gel permeation chromatography (GPC; Shanghai Kezhe Biochemical Technology Co., LTD, China). The chromatographic conditions were set as follows: chromatographic column: TSKgelgG2000SwxL300 mm × 7.8 mm (inside diameter); mobile phase: acetonitrile + water + trifluoroacetic acid (20 + 80 + 0.1, respectively); detection wavelength: 220 nm; flow rate, 0.5 ml/min; and detection time: 30 min. Peptide standard and SP powders were used to prepare a solution at a concentration of 1 mg/mL. The GPC data processing software was used to process and analyze the results, and the molecular weight distribution (range) of the peptide was obtained.

Effect of SP on Gentamicin-Induced Hair Cell Damage in Zebrafish

Zebrafish have inner ears and a mechanosensory lateral line system. The hair cells in both systems are homologous to those in mammals and show similar responses to ototoxic damage. Therefore, they are increasingly being used in auditory research [19,20].

Acute Toxicity of SP in the Zebrafish Model

In total, 300 wild-type AB strain of zebrafishes (5 days postfertilization) purchased from Shanghai Southern Model Biotechnology Co., Ltd. (Shanghai, China) were divided into 15 groups (n = 20, each). The control group was fed with normal fish water, and the other 14 groups received various concentrations of SP (0.1, 1.0, 2.5, 5.0, 10, 25, 50, 100, 250, 500, 750, 1000, 2500, and 5000 μg/ml). All zebrafishes were maintained at 28.5°C and a 14 h light/10 h dark cycle in fish water (0.2% Instant Ocean Salt in deionized water). After 24 h, the mortality of the zebrafish in each group was recorded. The mortality curve was generated using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA) and the LC50 was determined via logistic regression.

Grouping and Administration

Transgenic zebrafishes (5 days postfertilization; Shanghai Southern Model Biotechnology Co., Ltd.) having green fluorescent protein (GFP)-labeled hair cells (Brn3c:mGFP) were divided into four groups (n = 12, each)—control group (normal fish water), gentamicin group (5 mM gentamicin added to fish water), gentamicin + SP1 group (5 mM gentamicin and 100 μg/mL SP were added to the fish water), and gentamicin + SP2 group (5 mM gentamicin and 250 μg/mL SP were added to the fish water). The zebrafish were fed as described in section.

Observation of Hair Cell Damage

After 24 h, the lateral lines and head hair cells of each group were observed under an SMZ18 Fluorescence microscope (Nikon, Japan), and the images were quantitatively analyzed using image-based morphometric analysis (NIS-Elements D4.6, Japan) and the ImageJ software (U.S. National Institutes of Health, Bethesda, MD, USA).

Effect of SP on Gentamicin-Induced Nephrotoxicity in Mice

Animals and Ethical Approval

Thirty-five healthy and active c57BL/6J male mice (body weight: 18–19 g) having bright fur were obtained from the Hunan SJA Laboratory Animal Co., Ltd. (Hunan, China) and raised at our animal facility under pathogen-free conditions according to the institutional guidelines. The animal protocols were reviewed and approved by the Animal Care and Use Committee at the Henan Institute of Medical and Pharmaceutical Science. The animal experiments complied with the ARRIVE guidelines and were performed in accordance with the UK Animals Act.

Grouping and Administration

Gentamicin (100 mg/kg) was administered to the mice via the intraperitoneal (i.p.) route every morning, at the same time, 9.00 a.m. for 10 days. A total of 35 mice were split into five equal groups—control

group, gentamicin group (100 mg/kg), gentamicin + SP_1 group (100 mg/kg gentamicin [i.p] and 300 mg/kg SP [administered by gavage every other day]), gentamicin + SP_2 group (100 mg/kg gentamicin and 300 mg/kg SP [administered by gavage every day]), and gentamicin + SP_3 group (100 mg/kg gentamicin and 600 mg/kg SP [administered by gavage every other day]).

Sample Collection and Detection of Kidney Function Markers

On the 11th day of the experiment, all the mice were anesthetized using 10% chloral hydrate. The orbital blood was collected and centrifuged at 3850 r/min for 15 min. The supernatant was collected and stored in a refrigerator at −20°C to determine the levels of BUN, CRE, GSH, and T-AOC. Both kidneys were removed; one was placed in normal saline to detect the MDA and SOD levels and the other was fixed in 4% formaldehyde solution for histopathological examination.

Antioxidant Analysis

The kidney tissue (0.1 g) was cut into pieces using eye scissors and mixed with 0.9 ml of normal saline. The mixture was ground in a tissue homogenizer (IKA, Germany) and centrifuged at 2500 r/min for 15 min. The supernatant was obtained to determine the MDA and SOD levels. In addition, the levels of T-AOC and GSH in serum were measured using the respective enzyme-linked immunosorbent assay (Nanjing Jiancheng Bioengineering Institute Co., Ltd., Nanjing, China).

Histopathological Analyses

For histopathological analysis, the kidneys of the mice were fixed in 10% formalin solution for 4 h, dehydrated in graded alcohol solutions (70%–100%), soaked in xylene, followed by soaking in paraffin, and finally embedded in paraffin. The tissue-embedded paraffin blocks were cut into sections (5 μm), stained with Periodic Acid-Schiff (PAS), and then examined under a light microscope (Nikon Eclipse CI, Tokyo, Japan).

Statistical Analysis

One-way analysis of variance (ANOVA) was performed using the SPSS software package, Version 20.0. Data between groups were tested via ANOVA, and Tukey's post hoc test was used to compare the studied parameters between the groups. P-values <0.05 were considered significant. The results are expressed as mean ± standard error of the mean for each group.

Results

The Molecular Weight of SP

The molecular weight distribution of SP revealed a protein content of 94.3% and peptide content of 90.3% (small molecule active peptide content [≤1000 kd] was 83.4%; Table 1).

Table 1: The Molecular Weight Distribution of SP

Molecular weight (Da)	Peak area ratio (%, λ220 nm)	Number—average molecular weight	Weight—average molecular weight
>3000	2.93	4106	4521
3000–2000	3.29	2392	2425
2000–1000	10.28	1323	1373
1000–500	18.65	661	687
500–180	39.95	267	290
<180	24.89	-	-

Protective Effect of SP on Gentamicin-Induced Ototoxicity

Determination of LC50 of SP on Zebrafish

To investigate the toxic effects of SP in zebrafish, their survival upon exposure to different concentrations of the peptide was evaluated. As shown in Figure 1a, the death of juvenile zebrafish was observed at a concentration of 500 μg/ml. Figure 1b shows that the median lethal concentration of SP, obtained via regression analysis of the data in Figure 1a, was 677 μg/ml. Therefore, 100 and 250 μg/ml of SP were used for subsequent experiments.

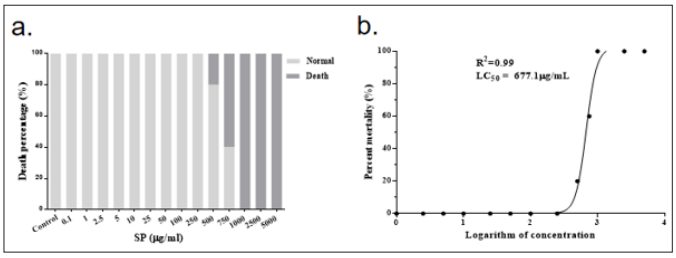

Figure 1: Acute toxicity of SP to Zebrafish (a) Death Percentage of Zebrafish after SP Treatment (b) Regression Analysis of Data from Panel (a).

Gentamicin-Induced Hair Cell Damage was Repaired by SP

The lateral lines and head hair cells of zebrafish were observed after the treatment with SP to assess the gentamicin-induced ototoxicity. As shown in Figure 2a, the nerve mounds on the hair cells (Green fluorescent dots) were significantly reduced after 24 h of gentamicin treatment (gentamicin group) when compared with those in the control group; however, the total number of nerve mounds in the 100 μg/ml- and 250 μg/ml-treated groups (gentamicin + SP_1 group and gentamicin + SP_2 group) were significantly higher than those in the gentamicin treatment group. The number of hair cells on the lateral line in the gentamycin group was significantly lower than that in the control group (Figure 2b; $P < 0.01$); the gentamycin + SP_1 group and gentamycin + SP_2 group had significantly more hair cells on the lateral line compared with the gentamycin group ($P < 0.05$ and <0.05, respectively). The number of hair cells on the heads of the zebrafish in the gentamycin group was significantly lower than that in the control group (Figure 2c; $P < 0.01$); the gentamycin + SP_1 and gentamycin + SP2 groups had significantly higher numbers of hair cells on the head than the gentamycin group ($P < 0.05$ and <0.05, respectively).

Therefore, the effect of SP on the number of hair cells on the lateral lines and head was similar.

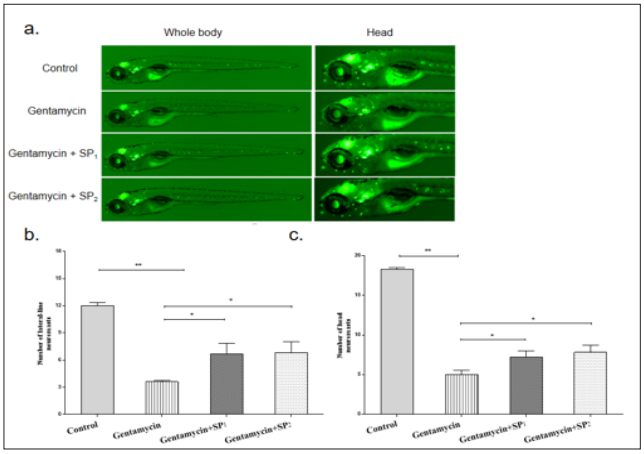

Figure 2: Hair cells in the zebrafish after treatment. (a) Fluorescence images of zebrafish hair cells; the left side shows hair cells in the whole body and the right side shows hair cells in the head). (b) Number of hair cells on the lateral line. (c) Number of hair cells on the head. *P < 0.05, **P < 0.01

Protective Effects of SP on Gentamicin-Induced Nephrotoxicity

Effect of SP on Gentamicin-Induced Kidney Function Damage

The serum CRE levels of the mice in the gentamicin group were significantly higher than those in the control group (Figure 3a; $P < 0.01$). However, following the administration of SP (300 mg/kg; gentamicin +SP_1 group), no significant difference in CRE level was observed when compared with that in the gentamicin group. Further increase in the dose of SP in the gentamicin + SP_2 and gentamicin +SP_3 groups resulted in significant reductions in serum CRE levels compared with that in the gentamicin group ($P < 0.05$ and $P < 0.05$, respectively).

Similar tendencies were observed with the levels of BUN in the same groups of mice. As shown in Figure 3b, the level of BUN in the gentamicin group was significantly higher than that in the control group (Figure 3b; $P < 0.01$). However, no significant difference was found between the gentamicin + SP_1 group and gentamicin group. Alternatively, significant decreases were observed in the gentamicin + SP_2 and gentamicin + SP_3 groups when compared with that in the gentamicin group ($P < 0.05$ and $P < 0.05$, respectively).

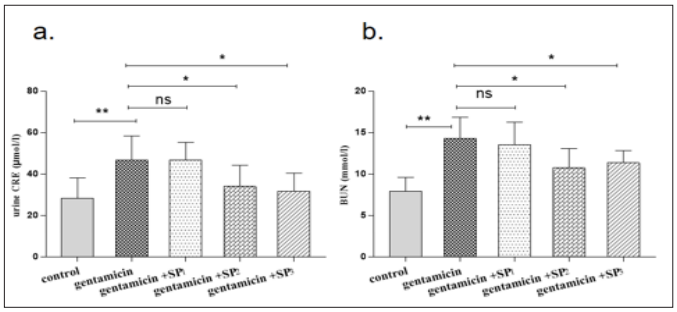

Figure 3: Levels of markers of kidney function. (a) Serum CRE level. (b) Serum BUN level. *$P < 0.05$, **$P < 0.01$

Effect of SP on the Antioxidant Property

As shown in Figure 4a, the MDA content in renal tissue homogenates was significantly higher in the gentamicin group than in the control group ($P < 0.01$). When SP was administered at 300 mg/kg (gentamicin +SP1 group), no significant difference in MDA content in renal tissue homogenate was observed when compared with that in the gentamicin group. However, the MDA content in renal tissue homogenates from the gentamicin + SP_2 and gentamicin + SP_3 groups were significantly lower than that in the gentamicin group ($P < 0.05$ and $P < 0.05$, respectively).

Interestingly, opposite effects were observed in the case of the three antioxidant markers (SOD, GSH, and T-AOC), as shown in Figures 4b, c, and d, respectively. The levels of the three antioxidant markers in the gentamicin group were significantly lower than those in the control group. No significant differences in levels were observed between the gentamicin +SP_1 group and the gentamicin group. Alternatively, the levels of the three markers in the gentamicin + SP_2 and gentamicin + SP_3 groups were significantly higher than those in the gentamicin group.

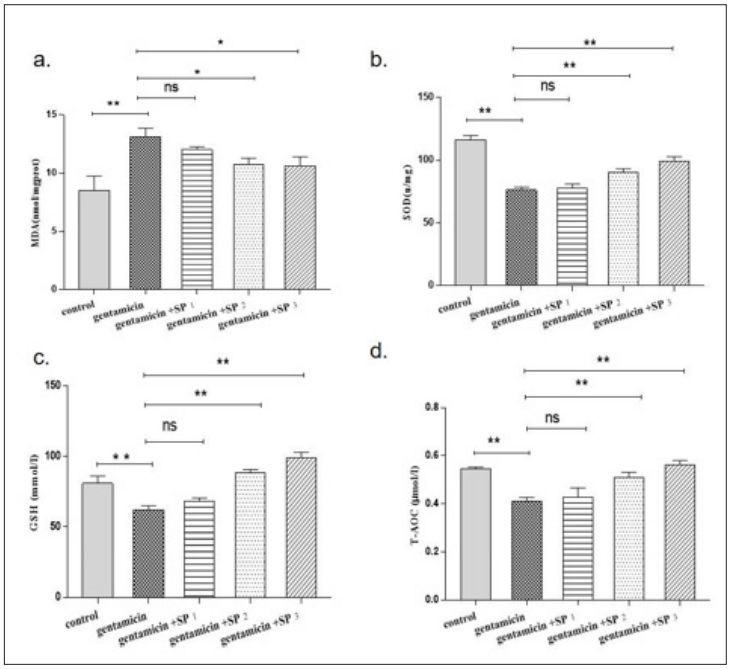

Figure 4: Antioxidant levels in the serum and renal tissues of the mice. (a) MDA content in renal tissue; (a) SOD content in renal tissue; (c) GSH content in serum; (d) T-AOC levels in serum. *$P < 0.05$, **$P < 0.01$

Effect of SP on Gentamicin-Induced Pathological Changes

The kidneys of mice in the control group with normal renal tubules and glomeruli were negatively stained for PAS (Figure 5a). The following changes were observed in the gentamicin group: swollen epithelial cells in the renal tubules, narrow lumen within the tubules, hyperplasia in the mesangial membrane of the glomerulus, and thickening of the basement membrane (Figure. 5b). The gentamicin + SP_1 group showed pathological characters similar to that in the gentamicin group (Figure 5c). A decrease in renal lesions was noted in the gentamicin + SP_2 group (Figure 5d) and gentamicin +SP_3 group (Figure 5e) mild swelling of the renal tubular epithelial cells was noted, and the thickening in the basement membrane was not obvious.

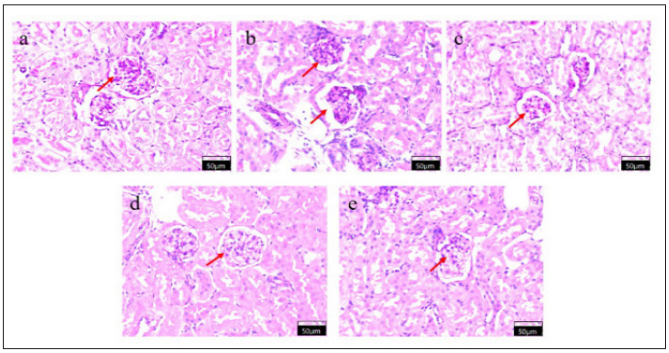

Figure 5: Pathological images of the renal tissues (×400). (a) Control group, (b) Gentamicin group, (c) Gentamicin +SP_1 group, (d) Gentamicin +SP_2 group, (e) Gentamicin +SP_3 group. The arrow points to the glomerulus

Discussion

The ototoxicity and nephrotoxicity of gentamicin in the clinical setting are well-known. Despite the constant development of new antibiotics, gentamicin continues to be used due to its low cost, broad antibacterial spectrum, and strong bactericidal effect [21]. However, it is important to administer the drug properly to reduce its toxicity.

The high affinity of the hair cells of the inner ear to gentamicin and the accumulation of gentamicin in the kidney are thought to be related to the development of gentamicin-induced ototoxicity and nephrotoxicity, respectively [12]. However, both ototoxicity and nephrotoxicity are essentially caused by the oxidative effects exerted by gentamicin. Studies have shown that gentamicin can induce excessive ROS production, destroy the antioxidant capacity of the cells, and cause lipid peroxidation and cell apoptosis [14,17]. A large number of apoptotic hair cells and increased oxidative stress were observed in zebrafish exposed to gentamicin [22]. Interestingly, SP is approved to have significant antioxidant activity and nontoxicity to human body. It can significantly eliminate ROS and inhibit cell apoptosis [2]. Intragastric administration of SP (600 mg/kg) improved the cognitive functions of mice with Alzheimer's disease by inhibiting oxidative stress [23]. Furthermore, the intragastric administration of SP (600 mg/kg and 1200 mg/kg) was reported to increase the antioxidant capacity and reduce the damage caused by alcohol, respectively, in mice [24]. Lunasin, a soybean bioactive peptide, is considered to be an important factor that inhibits the production of ROS and apoptosis [25,26].

In the present study, the administration of SP along with gentamicin demonstrated protective effects regarding both ototoxicity in zebrafish and nephrotoxicity in mice; moreover, the concentration of the SP was directly related to its efficacy. The number of hair cells of zebrafish damaged by gentamicin was greatly decreased at concentrations of 100 μg/ml and 250 μg/ml, and the kidney functions damaged by gentamicin in mice were partially restored at concentrations of 300 mg/kg every day or 600 mg/kg every other day. Moreover, the protective effect of SP was directly verified by the pathological characteristics of the kidneys damaged by gentamicin. The antioxidant levels were significantly increased after SP administration. These results prove that the protective effect of SP on both ototoxicity and nephrotoxicity caused by gentamicin is related to the antioxidant activity of the peptide. Other antioxidants such as Metformin have been found to act against gentamicin-induced toxicity and ameliorate oxidative stress in rats [27,28].

Conclusions

SP has good antioxidant properties and no toxic side effects on the human body. In addition, it is cheap and easily available. The gentamicin-induced ototoxicity and nephrotoxicity, which is essentially caused due to excessive production of ROS, was decreased following the administration of SP in the zebrafish and mice in the current study. These findings indicate the protective role of SP and it may be considered for use during clinical treatment in the future. Although many animal experiments and cytological studies of soybean peptides have been reported, we are the first to study the effects of soybean peptides in zebrafish and have made important findings

Acknowledgements

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Ethics Approval and Consent to Participate

All animal experiments were in accordance with the standards set forth in the eighth edition of Guide for the Care and Use of Laboratory Animals (published by the National Academy of Sciences, The National Academies Press, Washington, D.C.). All animals were kept in a pathogen-free environment. The procedures for care and use of animals were Approved by the Ethics Committee of the Zhengzhou University and all applicable institutional and governmental regulations concerning the ethical use of animals were followed.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Author Contributions

Xinling Wang and Puyun You performed most of the experiments and data analysis. Xinling Wang and Puyun You wrote the paper. Guanglei Chang, Zhaobin Xu and Miaomiao Yang contributed to the data analysis and prepared the figures. Wenyao Li analysed the images. Kuicheng Zhu was responsible for supervision and data curation. Liguo Zhang and Meixia He designed the study and provided assistance with the experiments and manuscript preparation. All authors reviewed the data and approved the final version of the manuscript.

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