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Antioxidant capacity of sesamol in *Caenorhabditis elegans* model system

Jinian Huang[1*], Shuning Qi[2], Qiang Sun[1], Guohui Song[1], Jixing Tang[2] and Yuquan Duan[2*]

Abstract

Senescence is a general and irreversible process which depends on both inherent (free radical and age) and external (Ultraviolet irradiation) factors. Antioxidants and other natural compounds like plant and plant products are widespread use for their medicinal and therapeutic values. The present study focuses on the role of sesamol which has been used to delay the effects of photoaging using model nematode *Caenorhabditis elegans* (*C. elegan)* by measuring the longest life, average life, reproductive capacity, and the variation of reactive oxygen of *C. elegans* under different stress conditions. The result showed that 200 μg·mL^{-1} sesamol significantly extended the life of *C. elegans*, that is, the mean lifespan of the treatment groups were 43.3% longer than control group. Meanwhile, sesamol significantly prolonged the lifespan of *C. elegans* under heat stress, ultraviolet irradiation stress, and oxidative stress. Above all, sesamol could be used as potential antioxidant compounds which will be of greater significance for health-based research.

Keywords Sesamol, Antioxidant, Lifespan, Reactive oxygen species, *Caenorhabditis elegans*

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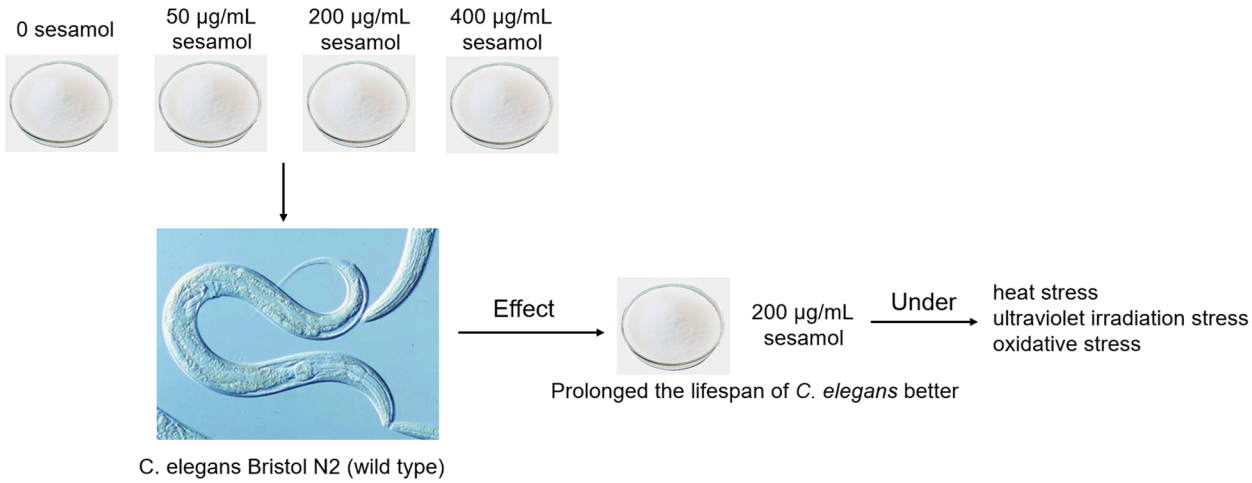
Graphical Abstract



Introduction

Sesamol is a kind of polyphenol lignan found in sesame seeds and oil. It has been proved to exert a variety of pharmacological functions such as anti-tumor, liver protection, regulation of cholesterol metabolism, and maintenance of blood pressure (Sharma et al. 2012; Liu et al. 2017; Rishi et al. 2017; Ananieva and Belinska 2019). At present, a number of researches have focused on investigating the high-efficiency physiological activity of sesamol, most of which are limited to scavenging free radicals in vitro, inhibiting tumor cell growth, and antioxidant properties (Castrogonzález et al. 2021; Majdalawieh et al. 2019) However, the underlying mechanisms have not been fully elucidated.

There is an increasing in evaluation of antioxidant properties of natural bioactive compounds in vitro and in vivo. *Caenorhabditis elegans* (*C. elegans*) has been favored for its simple structure, complete development, and facilitation to perform gene deletion analysis (Liu et al. 2019). *C. elegans* has the characteristics of being transparent and easy to observe under a microscope, long-term storage, and short survival time (Ann et al. 2015). As a model organism in aging and antioxidant research, *C. elegans* has incomparable advantages and becomes the preferred model for studying the physiological activities of natural products (Chen, 2012; Duhon et al. 2015). In recent years, the relevant studies began to evaluate the antioxidant activities of polyphenols, flavonoids and other substances by *C. elegans* (Dilberger et al. 2021; Hu et al. 2021). However, the information of antioxidant properties and anti-aging mechanisms of sesamol in *C. elegans* model is limited.

In order to evaluate the anti-aging effects of sesamol and its property to protect organism against oxidative stress, *C. elegans* was used as the model and the effects of sesamol on the lifespan and antioxidant capacity were investigated.

Materials and methods

Materials

C. elegans Bristol N_2 (wild type)

Hermaphrodite, gifted by the National Institute of Biological Sciences, Beijing.

+E. coli OP50

A uracil-deficient strain, coated on the surface of the culture medium, as food for *C. elegans*, gifted by the National Institute of Biological Sciences, Beijing.

Sesamol

Extracted in the laboratory of Agricultural Products Processing Institute, Henan Academy of Agricultural Sciences, with a purity of 97.8%.

Extraction method of Sesamol sample

Sesamol was extracted according to the extraction method of Huang (2008). Use sesame oil to extract sesamol. First, extract sesamol. Before extraction, shake sesame oil well. Add 1500 mL to the extraction column. Each time, add 2000 mL absolute ethanol for countercurrent extraction, until a filter strip is dipped in the extraction solution. After drying, no color is detected under the ultraviolet lamp. Then, use the rotary evaporator to

evaporate the extraction liquid until there is no ethanol distillate. Use 100 L absolute ethanol to extract 1 L extract from 5 L sesame oil, and seal it at low temperature for column chromatography. Then carry out column chromatography separation, take a certain amount of extract, dissolve it with sufficient ethyl acetate, place it in the refrigerator, separate out dark black solids, take 6 g of solids for chromatography, elute with petroleum ether ethyl acetate gradient, collect some components of sesamol, dry it, and get sesamol samples.

General cultivation of *C. elegans*

Cultivation of E. coli OP50

Shake culture of OP50 strains in 100 mL LB liquid medium for 12 h until OD600 = 0.4 for inoculation of Nematode Growth Medium (NGM) plates to feed *C. elegans*.

Cultivation of C. elegans

Small pieces of *C. elegans*-containing medium were cut under aseptic conditions and placed in a new petri dish, which was cultivated at 20 °C, humidity of 40-60%. An agar plate with a smooth surface and no bubbles or scratches was chosen to prevent *C. elegans* from drilling into the medium through the surface when cultivating. For subculture of a small number of *C. elegans*, placed a hermaphroditic *C. elegans* in the egg-laying stage on NGM medium coated with *E. coli OP50*, and cultured under standard culture conditions. For subculture of a large number of *C. elegans*, cut a piece of medium containing more *C. elegans* from the medium with a scalpel blade that has been sterilized, and transfer it to the NGM medium coated with *E. coli*. The *C. elegans* automatically moved to the direction with more food to complete the subculture of *C. elegans*. (Goldstein & Bob 2016; Kohl et al. 2018)

Synchronization of C. elegans

Time-limited oviposition

When a small number of *C. elegans* need to be synchronized, several *C. elegans* in the oviposition period were selected and put in a new medium. Each *C. elegans* in the oviposition period laid 4–8 eggs per hour. after culturing for 30 min under standard conditions, the *C. elegans* in the plate were picked out and the eggs in the plate were at the same developmental stage.

Bleaching with sodium perchlorate

When a large number of *C. elegans* need to be synchronized, prepare 2–3 plates where more than 80% of the insects in the plates are in the reproductive period, and proceed as follows: (1) Take 5 ml of M9 buffer to wash the plates twice, suck the M9 buffer containing insects into a 10 ml centrifuge tube, centrifuge at 1200 rpm for 3 min, and discard the supernatant; (2) Add 5 ml of freshly prepared synchronized bleaching solution, shake vigorously at room temperature for 3 min to corrode the adult insects, and tiny eggs can be seen under the microscope. Centrifuge at 1200 rpm for 2 min, and discard the supernatant; (3) Add 5 ml M9 buffer to suspend the precipitation, centrifuge at 1200 rpm for 2 min after mixing, discard the supernatant, wash 4 times; (4) Centrifuge for the last time, leave about 2 ml of the solution when discarding the supernatant, and shake well; (5) Pour the solution into a petri dish that has not been inoculated with OP50 and cultivate at 20 ℃ for 18–24 h. (Ozpinar 2020).

Transfer the larvae to a growth plate (10–20 μL per plate) to obtain synchronized *C. elegans*.

The effect of sesamol on the lifespan of *C. elegans*

Sodium perchlorate bleaching method was used to synchronize *C. elegans* grew to the L4 stage which were then selected and put in 55 mm plates which contained 50 $\mu g \cdot mL^{-1}$, 200 $\mu g \cdot mL^{-1}$, and 400 $\mu g \cdot mL^{-1}$ sesamol. The plates were coated with OP50 solution. The group without sesamol added was regarded as the control. The number of *C. elegans* in each group was not less than 60, and this time was counted as the 0th day of the lifespan experiment of *C. elegans*. Transferred the *C. elegans* to a new petri dish every other day until the *C. elegans* no longer lay eggs (usually about 10 days). Observed the *C. elegans* every day and recorded their survival, death, and elimination numbers until there was no one alive. Judgment criteria for death: use platinum wire to touch the body to see if there is any reaction, movement or swallowing; judgment criteria for elimination: *C. elegans* climbed to the wall of the petri dish or the lid of the petri dish and died, or drilled into the agar and cannot grow normally. The test plates all contained 50 μM 5-fluoro-2'-deoxyuridine (FUDR) to limit the hatching of offspring larvae. The above experiment was repeated at least twice, and the survival rate was statistically analyzed (Beaudoin-Chabot C. 2019).

The effect of sesamol on the reproduction of *C. elegans*

Synchronize *C. elegans* with the time-limited oviposition method. Two days later, The *C. elegans* from same growth state were selected and put in 55 mm plates which contained 50 $\mu g \cdot mL^{-1}$, 200 μg·mL-1, and 400 $\mu g \cdot mL^{-1}$ sesamol and were coated with OP50 solution. The group did not contain sesamol as the control. The number of *C. elegans* in each group was not less than 10. Place 1 *C. elegans* in each NGM petri dish, and transferred the

C. elegans to a new petri dish every 24 h until the *C. elegans* no longer laid eggs. All the petri dishes were cultured under standard culture conditions, and the number of *C. elegans* was counted before the offspring entered the oviposition period. Generally, the number of eggs laid by each *C. elegans* was counted on the second day after laying eggs, and the sum is the number of eggs laid by the *C. elegans*. The above experiment was repeated at least twice, and statistical analysis was performed.

Stress test of *C. elegans*

According to the method of Wilson (2006), the hermaphrodite *C. elegans* in the egg-laying stage were picked out and put into a blank petri dish and NGM petri dish containing 50 $\mu g \cdot mL^{-1}$, 200 $\mu g \cdot mL^{-1}$, and 400 $\mu g \cdot mL^{-1}$ sesamol for 0.5 h of oviposition, and the resulting larvae were incubated for 59 h under standard conditions to develop into adults. Then the adults were exposed to different environmental conditions to study the protective effects of the drugs on the *C. elegans* under environmental stress. The number of *C. elegans* in each group was not less than 60, and the experiment was repeated at least twice.

Acute heat stress test

According to the method of Hansen (2005), the adult *C. elegans* after treatment were cultured in an incubator at 35 ℃, and the number of survived, dead, and eliminated *C. elegans* were recorded every 1 h until all the *C. elegans* died. The counting standard for each group was the same as that of the lifespan test.

Oxidative stress test

According to the method of Duhon et al. (1996), hydrogen peroxide was selected as the oxidant, and the adult *C. elegans* after treatment were put into a 12-well plate containing 4 mM hydrogen peroxide M9 buffer, and the number of survived and dead *C. elegans* were recorded every 1 h until all the *C. elegans* died. Judgment criteria for death: platinum wire to touch the body was touched with platinum wire to see if there was any reaction.

Ultraviolet irradiation stress test

According to the method of Vayndorf (2013), the adult *C. elegans* after treatment were radiated under a UV lamp for 90 s. The UV lamp was 15 cm from the culture plate and the power was 30 W. The number of survived, dead, and eliminated *C. elegans* were recorded every 8 h until all the *C. elegans* died. The counting standard for each group was the same as that of the lifespan test.

Determination of reactive oxygen species (ROS) in *C. elegans*

The detection of ROS in *C. elegans* was performed by H2DCF-DA molecular probes (Wu et al. 2011). The treatment group was treated with sesamol for 48 h and the control group was not treat with sesamol. Then M9 buffer was used to collect the *C. elegans* and placed them in a 1.5mL EP tube, and then 50μL molecular probes (final concentration was 50 μM) were added after transferring to a black 96-well plate (50μL per well). Then a water bathing was conducted at 20 ℃ for 30 min. The fluorescence enzyme labeling method was used to detect the fluorescence intensity under a filter with excitation wavelength of 485 nm and emission wavelength of 538 nm. The detection was performed every 30 min for 2 h.

Statistical analysis

Statistical tests on physiological data were performed through analysis of variance, and Duncan's Multiple Range test was used for mean comparison ($P < 0.05$). SPSS 24.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and Origin 8.6 (Microcal Software, Northampton, MA) was used to prepare figures. The results represent mean ± standard error of three replicated determinations.

Results

The effect of sesamol on the lifespan of *C. elegans*

We found that all chosen test concentrations of sesamol were non-toxic to C. elegans. The mean lifespan of wild-type *C. elegans* under standard culture conditions was 14–21 days. When *C. elegans* were treated with 50 $\mu g \cdot mL^{-1}$, 200 $\mu g \cdot mL^{-1}$, and 400$\cdot \mu g \cdot mL^{-1}$ sesamol, the lifespan of the *C. elegans* was significantly prolonged. The longest lifespan of the corresponding treatment groups was 31 days, 37 days and 33 days, respectively. Compared with the control group, the longest lifespan of *C. elegans* in the sesamol treated group was extended by 4 days, 10 days and 6 days, respectively (as shown in Fig. 1).

The mean lifespan of wild-type *C. elegans* was 18 days, while the sesamol treated groups (50 $\mu g \cdot mL^{-1}$, 200 $\mu g \cdot mL^{-1}$, and 400 $\mu g \cdot mL^{-1}$ sesamol) had a mean lifespan of 20 days, 27 days and 23 days, respectively, which was 15.3%, 44.3%, and 29.4% longer than that of the control ones (as shown in Fig. 2).

The lifespan increased with the increasing concentration of sesamol, when the concentration of sesamol was 200 $\mu g \cdot mL^{-1}$, it showed the most significant improvement (44.3%), then, decreased with increase in the concentration of sesamol. Similar results were obtained using a crude extract of with anolide A (Akhoon et al.

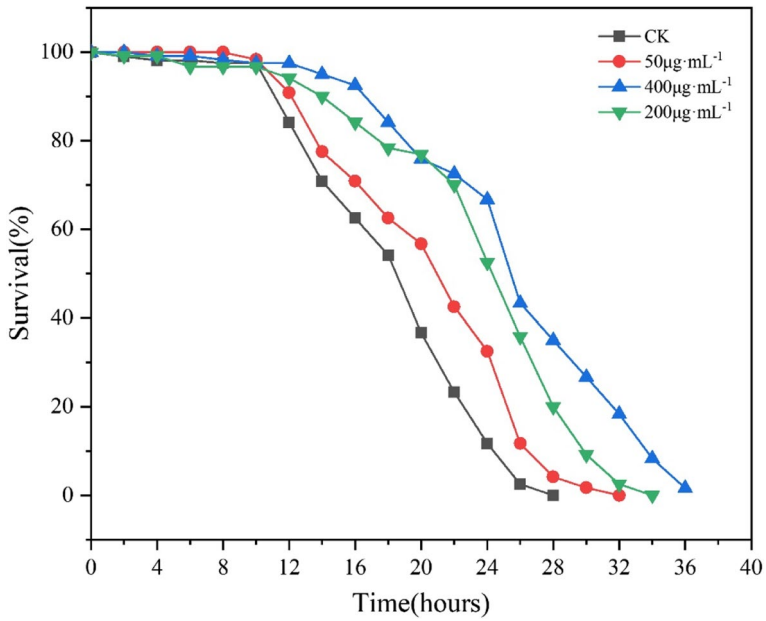


Fig. 1 Effect of sesame lignans extracts on the lifespan of *C. elegans*

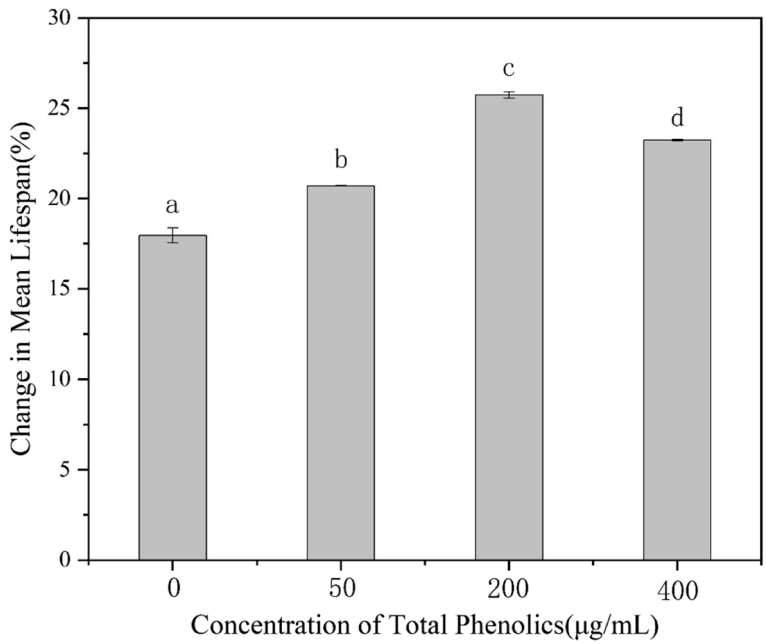


Fig. 2 Effect of sesame lignans extracts on the mean lifespan of *C. elegans* (Different letters means significantly different from each other at $p = 0.05$)

2016), when it comes to explore natural products for antioxidant and antiaging potentials (Büchter et al. 2013).

The effect of sesamol on the reproductive ability of *C. elegans*

In this experiment, the total number of eggs laid by wild-type *C. elegans* in the control group was 178 ± 36, which in the sesamol treated groups (50 $\mu g \cdot mL^{-1}$, 200 $\mu g \cdot mL^{-1}$, 400 $\mu g \cdot mL^{-1}$ sesamol) was 219 ± 39, 196 ± 44 and 150 ± 31, respectively (as shown in Fig. 3). The total number of eggs laid by *C. elegans* in the 50 $\mu g \cdot mL^{-1}$ and 200 $\mu g \cdot mL^{-1}$ sesamol treatment groups was significantly higher than that of the control group, but the 400 $\mu g \cdot mL^{-1}$ sesamol

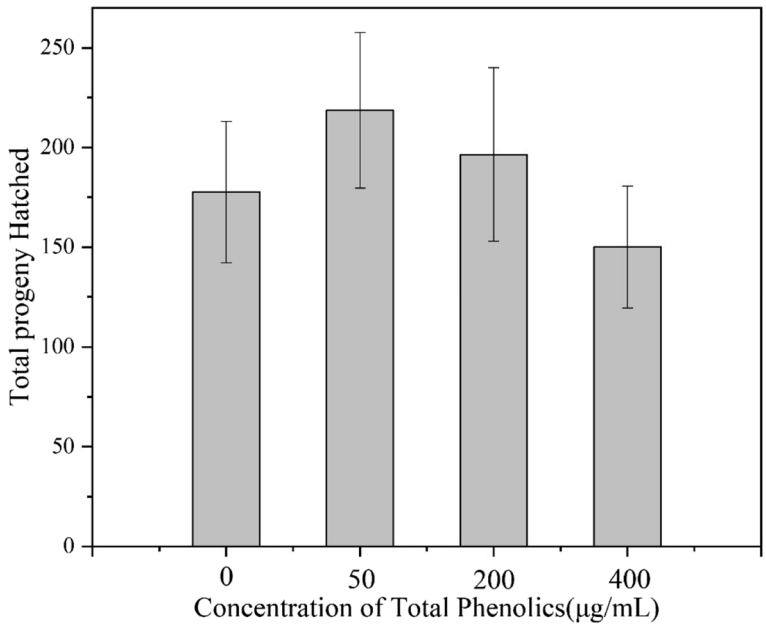


Fig. 3 Effect of sesame lignans extracts on the number of progeny produced of *C. elegans*

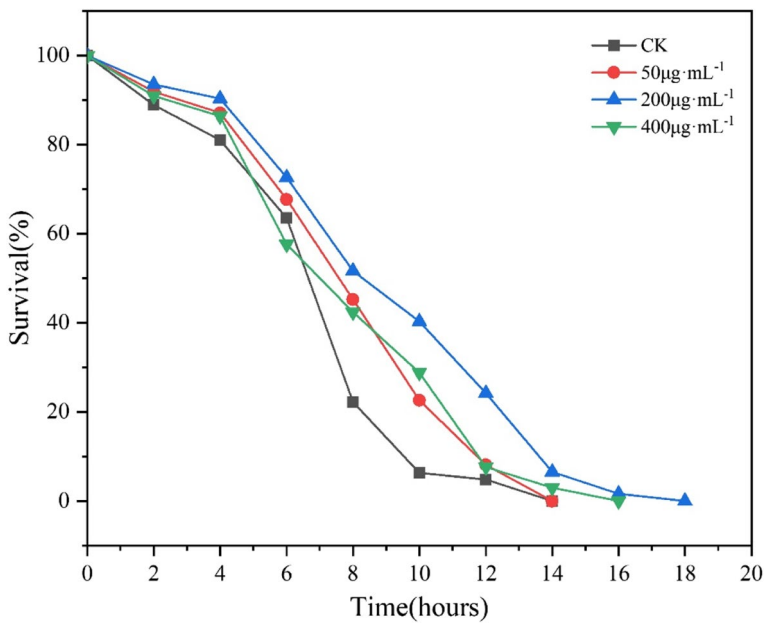


Fig. 4 Effect of sesame lignans extracts on resistance to hot stress in *C. elegans*

treated group had the lowest eggs. The results suggested that there was no significant difference in the number of eggs laid between the treatment groups and the control group, so sesamol had no significant effect on the reproductive ability of *C. elegans*.

The effect of sesamol on the resistance of *C. elegans* to oxidative stress

Acute heat stress test

Heat treatment can lead to the death of *C. elegans* which is one of the most important reasons of

oxidative damage (Chen, 2012). To evaluate the effect of on thermotolerance, the *C. elegans* were administered and then placed in an incubator at 35 °C. As shown in Fig. 4, the survival rate of *C. elegans* in the treatment groups (50 μg·mL^{-1}, 200 μg·mL^{-1}, and 400 μg·mL^{-1} sesamol) significantly increased under heat stress, and the increase rate was respectively 16.1%, 29.1%, and 16.3%, the longest life span increased from 13 h in the control group to 14 h, 17 h and 15 h. Among them, the 200 μg·mL-1 treatment group had the best protective effect.

Oxidative stress test

Hydrogen peroxide (H_2O_2) was used to cause oxidative damage to *C. elegans*. The *C. elegans* in the sesamol treated groups were pretreated with 50 μg·mL^{-1}, 200 μg·mL^{-1}, 400 μg·mL^{-1} sesamol for 59 h, and then were put into a 12-well plate containing 4 mM hydrogen peroxide M9 buffer for oxidative stress.

The mean lifespan of *C. elegans* in the control group was 6.45 h, and the mean lifespan of the sesamol treated groups was 7.69 h, 8.98 h, and 7.91 h, respectively (as shown in Fig. 5), which was 19.2%, 38.6% and 22.66% longer than that of the control group. When the concentration of sesamol was 200 μg·mL^{-1}, the *C. elegans* ability to resist the oxidative damage of hydrogen peroxide was significantly improved, and the sensitivity to hydrogen peroxide was reduced. These results indicated that sesamol significantly improves *C. elegans*' resistance to oxidative stress (Pandey et al. 2018).

Ultraviolet irradiation stress test

Ultraviolet irradiation can disrupt the normal growth and development of *C. elegans* and induce them to produce reactive oxygen species (Prasanth et al. 2020). In this study, *C. elegans* were pretreated with 50 μg·mL^{-1}, 200 μg·mL^{-1}, and 400 μg·mL^{-1} sesamol for 59 h, and then irradiated with ultraviolet light. Results showed that sesamol could protect *C. elegans* from ultraviolet irradiation stress, and significantly prolong their mean and maximum lifespan. The mean lifespan of the 50 μg·mL^{-1}, 200 μg·mL^{-1}, and 400 μg·mL^{-1} sesamol treated groups was 55.89 h, 61.87 h and 57.81 h, respectively (as shown in Fig. 6). Compared with 41.81 h in the control group, the lifespan was extended by 33.7%, 48.0% and 38.3%, respectively. Same as the situation in heat stress test and oxidative stress test, when the concentration was 200 μg·mL-1, sesamol had the best effect to protect against ultraviolet irradiation stress.

The effect of sesamol on the reactive oxygen species level in *C. elegans*

ROS is one of the important factors to determine the body's normal physiological balance.(Vergara-Salinas 2015) If the content of ROS is lower than the equilibrium point, the functions of cell defense and cell proliferation will be affected. On the contrary, a higher level of ROS will cause harm to cells and even lead to cell death and diseases such as atherosclerosis and cancer. (Ruangchuay et al. 2021; Xiao et al. 2014) H2DCF-DA molecular probe was used to detect the scavenging effect of sesamol on ROS in *C. elegans*.

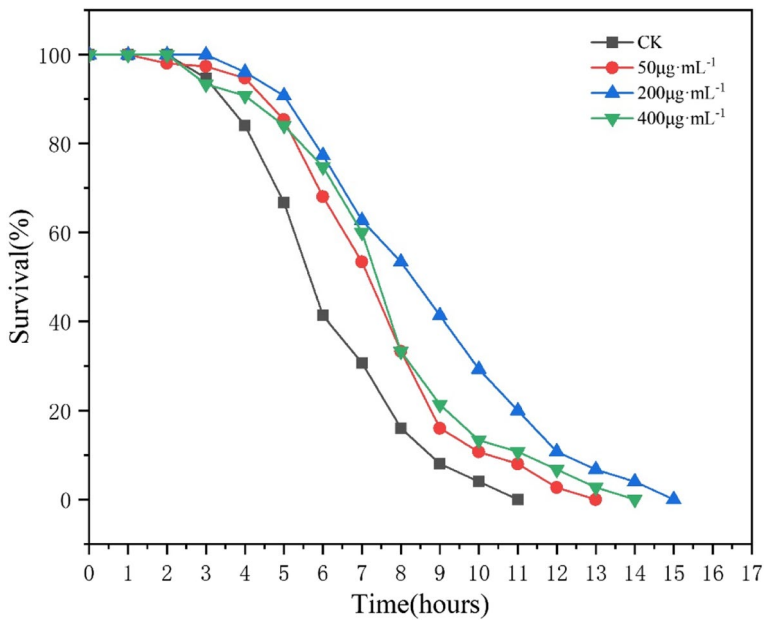


Fig. 5 Effect of sesame lignans extracts on resistance to oxidative stress in *C. elegan*

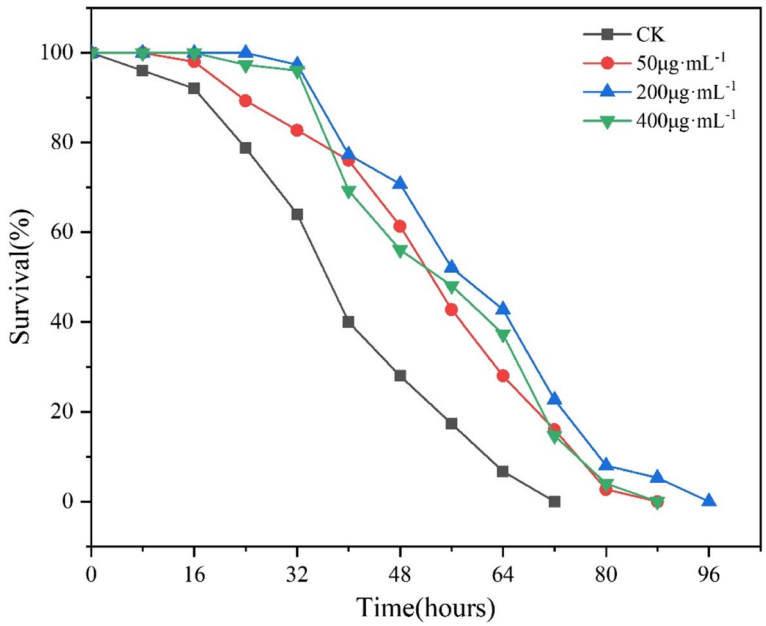


Fig. 6 Effect of sesame lignans extracts on resistance to UV irradiation in *C. elegans*

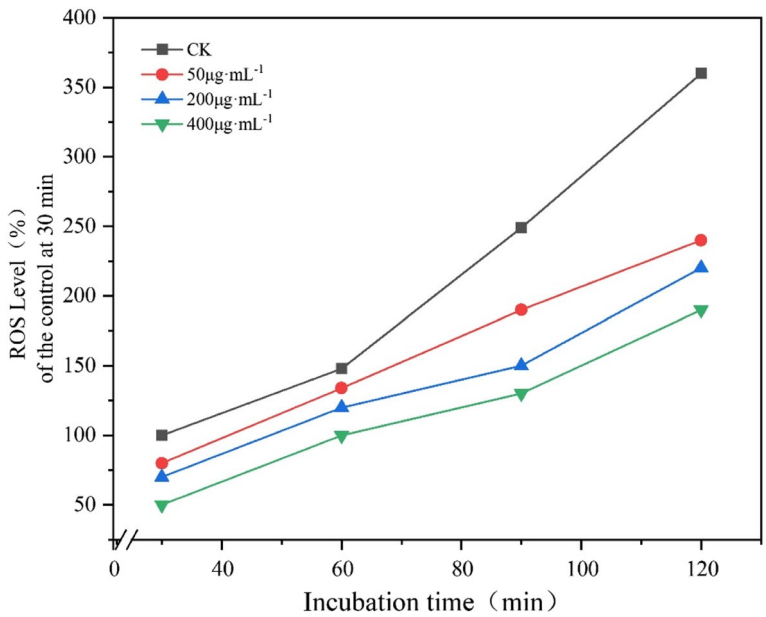


Fig. 7 Effect of sesame lignans extracts on ROS in *C. elegans*

The results were shown (as shown in Fig. 7) ROS level in the *C. elegans* increased with the extension of the culture time. Compared with the control group, sesamol significantly inhibited the increase of reactive oxygen species in the *C. elegans*. And there is a negative correlation between the sesamol concentration and the ROS level, that is, the higher the sesamol concentration, the more significant the scavenging effect of ROS in *C. elegans* ($p<0.05$) (Zhang et al. 2020).

Conclusion

Sesamol which is a natural food functional factor with strong antioxidant activity shows an immense medicinal and therapeutic potentials (Zhou 2021). This study

reveals that sesamol not only significantly prolonged the lifespan of *C. elegans* but decreased endogenous ROS level, increased antioxidant enzyme activities, and reduced lipid peroxidation product content of nematodes. When treated with 200 $\mu g \cdot mL^{-1}$ sesamol, the lifespan of *C. elegans* was extended under abiotic stress (heat stress, ultraviolet irradiation stress and oxidative stress) because a certain concentration of sesamol has a strong free radical scavenging ability (Kushwaha 2020). Our research results are in agreement with the finding of other research groupes which reported that sesamol extended lifespan in C. elegans model (Yukie et al. 2014; Roongpetch et al. 2018).

These results showed that sesamol could increase its resistance to environmental stress and as potential natural additives to enhance the stability of lipid oxidative of edible oil (Grünz et al. 2012; Gong et al. 2012). In view of the short life cycle and clear genetic background of *C. elegans*, the mechanism of the biological activity of sesamol can be further studied, and the inner link between antioxidant mechanism and biological activity can be further clarified, providing a theoretical basis for the development of sesamol health products and related drugs.

Abbreviations

C. elegan	Caenorhabditis elegans
NGM	Nematode Growth Medium
FUDR	5-fluoro-2′-deoxyuridine
ROS	Reactive oxygen species
H2O2	Hydrogen peroxide

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Not applicable.

Authors' contributions
GS and JT performed the experiment; SQ and QS contributed significantly to analysis and wrote the manuscript; JH and YD contributed to the conception of the study and helped perform the analysis with constructive discussions.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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