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# Resveratrol Protects *Caenorhabditis elegans* from Ultraviolet B-induced Photoaging via *skn-1*

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**Background:** Resveratrol (RSV) is a polyphenol with potent antioxidant activity and is abundant in fruits. There has been a lot of scientific evidence regarding the anti-aging effect of RSV. Aging can be induced by UV-B (photoaging) due to the production of reactive oxygen species (ROS) and oxidative stress. This study aimed to test the anti-photoaging activity of RSV on UV-B -induced *Caenorhabditis elegan*s.

**Materials and methods:** *C. elegans* was cultured at 20˚C in nematode growth medium (NGM) and was subjected to various concentrations of RSV and UV-B. The UV-B light exposure was given on day 0 post-synchronization at a dose of 100 J/m$^2$ using a UV cross-linker. The health span (indicated by pharyngeal pumping rate) and lifespan of worms were observed. The quantification of collagen was performed using a Sircol Collagen assay kit. The mRNA expression level of *gcs-1*, *col-19*, *hus-1*, *cep-1*, *egl-1*, and *ced-13* was examined by qRT-PCR.

**Results:** UV-B reduced pharyngeal pumping rate, shortened the lifespan, decreased collagen, and increased the expression of apoptosis-related genes (*hus-1*, *cep-1*, *egl-1*, and *ced-13*). RSV ameliorated these aging phenotypes induced by UV-B. Anti-aging activities of RSV were not observed in the *skn-1* loss-of-function strain (VC1772, *skn-1*(ok2315)), indicating the critical involvement of *skn-1* in the mechanism of action of RSV. The activation of *skn-1* was shown by elevated *skn-1* target gene that play role in glutathione biosynthesis called *gcs-1*.

**Conclusion:** RSV prevents accelerated aging due to UV-B in *C. elegans* by enforcing *skn-1* signaling pathway and its downstream *gcs-1* gene expression.

**Keywords:** *anti-aging, resveratrol, oxidative stress,* UV-B

## Introduction

The elderly population in Indonesia is expected to increase by 8% by 2040, with a projected increase in life expectancy from 73.37 to 76.56 in 2050.[1] However, data shows that despite the increase in life expectancy, the number of healthy years (healthspan) has not shown the same level of improvement, where patients have poor health for a long period of time and often experience various degenerative conditions.[2] Indonesia has a greater responsibility to guarantee the population healthy elderly in the future.

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One of the most dominant causes of aging is free radicals. Free radicals are molecules that have unpaired electrons, high reactivity, and cause damage to macromolecules such as DNA, fat, and protein, causing disruption of cell function, even cell death.[3] The condition of increased free radicals in the body is called oxidative stress. Oxidative stress can be caused by various conditions, such as ultraviolet (UV) radiation. UV-A (315-340 nm) and UV-B (280-320 nm) rays in sunlight can increase various superoxide radicals, hydrogen peroxide, and hydroxyl radicals and then cause photooxidation reactions. Prolonged exposure to UV light causes photoaging, shown as wrinkle development, age spots or hyperpigmented lesions, and a decline in the integrity of skin tissue.[4] Skin disintegration and decreased collagen synthesis are major signs of photoaging. Collagen activity is affected by UV radiation, the existing collagen in extracellular matrix would be degraded and the production of new collagen will be impeded as the amount of UV exposure rises.[5]

Moreover, apoptosis is typically triggered by UV radiation, both death receptors and mitochondrial apoptotic pathways. The *cep-1* of *C. elegans* is ortholog to human p53, primarily facilitating apoptosis. The *hus*-1 is required for DNA damage-induced cell cycle arrest and death because it activates the traditional apoptotic pathway controlled by *cep-1*. The transcription of the pro-apoptotic genes *egl-1* and *ced-13* is triggered upon the activation of the *cep-1*-mediated apoptotic pathway. By inhibiting the actions of anti-apoptotic BCL-2 family members, the *egl-1* causes apoptosis induction. Furthermore, when overexpressed, *ced-13*, the sole protein in *C. elegans* with a BH3 domain, interacts with *ced-9* to induce apoptosis. The control of UV-induced apoptosis in *C. elegans* is mediated by these four genes.[6,7]

To prevent premature aging due to UV-B-induced oxidative stress, antioxidants are needed that can come from within the body as a natural response and also supplementation from outside the body. Resveratrol (RSV) is a naturally occuring polyphenol compound found in various foods such as grapes, red and white wine, raisins, peanuts, pistachios, white currant, blueberries, cranberries, and even cocoa and dark chocolate. Many studies have shown that resveratrol has antioxidant, vasoprotective, cardioprotective, anti-inflammatory, anti-cancer, anti-obesity, and anti-aging effects.[8] Several studies have shown that RSV has activity as a primary antioxidant (giving or receiving electrons directly) and secondary (activating the cellular antioxidant system).[9] RSV increases the cellular antioxidant system through the activation of the transcription factor Nrf2, which is a regulator of antioxidant genes.[9,10] The mechanism of action of RSV is by activating autophagy to degrade Keap1, a protein that inhibits the work of Nrf2.[11] Scientific evidence of RSV's antioxidant activity is very strong and antioxidant was well-known to have a strong correlation with anti-aging activity, but the effect of RSV on lifespan and healthspan is still controversial. Several studies have reported that RSV does not increase the lifespan of healthy experimental organisms, but RSV can increase the lifespan of experimental animals with metabolic disorders or environmental factors.[12,13]

RSV has been shown to increase the lifespan of C. elegans through the Sirtuin pathway and ERK.[14,15] However, until now there has been no study linking RSV anti-aging activity with cell antioxidant activity and response. In *C. elegans*, the function of Nrf2 is orthologous to SKN-1.[16,17] SKN-1 regulates the expression of phase II gene *gcs-1*, ortholog of human GCS, which is a representative and well-characterized Nrf2/SKN-1 target gene.[18] The gcs-1 enzyme is crucial for oxidative stress resistance by acting as rate-limiting for glutathione synthesis.[19] The purpose of this study was to examine RSV effect on photoaged *C. elegans* induced by UV-B and to understand the role of SKN-1/Nrf2.

## Materials and methods

### *Caenorhabditis elegans Culture*

The *C. elegans* was used as a model organism in this study and was obtained from the Caenorhabditis Genetic Center (CGC), Minneapolis, MN. In the present study, wild-type reference N2 Bristol, and VC1772 [*skn-1*(ok2315)] strains were used. All nematodes were cultured at 20˚C in nematode growth medium (NGM) supplemented with *E. coli* strain OP50 using standard techniques.

### *Treatments of C. elegans*

For RSV (Sigma Chemical Co., St. Louis, MO, USA) treatment, RSV solution in DMSO was added to NGM at a final concentration of 50, 100, or 200 μM. In the UV-B irradiated nematode group, UV-B light exposure was given on day 0 post-synchronization at a dose of 100 J/m$^2$ using a UV cross-linker (JRA03-II, Jieruian, WuXi, China).

### *Examination of Lifespan and Health Span*

Lifespan calculation was performed on post-synchronization hermaphrodites using the sodium hypochlorite method; the final L4 larvae were removed and designated as experimental day 0. Nematodes were transferred to a new

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culture medium and scored every two days for lifespan observation. Nematodes that did not respond to touch stimuli were considered dead, while nematodes that were lost were censored. For healthspan examination using the pharyngeal pump rate indicator, nematodes on days 7 and 12 were observed individually using a TCS SP8 stereo microscope (Leica Microsystems, Wetzlar, Germany) and recorded digitally (VLC, ver. 2.1.3) on the NGM. The pharyngeal pump rate was calculated manually by playing a 30-second video. The pharyngeal pumping is defined as the contraction of corpus (seen as an opening of lumen of the anterior pharynx) and the relaxation of terminal bulb synchronously. The unit of counting is times per minute.

***Measurement of Collagen Content***

Sircol™ Collagen assay kit was used to quantify the amount of collagen within the worms' body. In brief, 50 µg of total protein was obtained from worm lysates and was incubated for 30 minutes with Sircol dye. Additionally, the proteins were centrifuged and excess dye was removed using a particular acid-salt reagent. After further dissolving the pellet in alkali reagent, the absorbance at 555 nm was measured and plotted against a standard graph

***Quatification of mRNA Levels***

Gene expressions (*gcs-1*, *col-19*, *hus-1*, *cep-1*, *egl-1*, and *ced-13)* were performed using RT-qPCR. Total RNA was isolated using Isogen (Nippon Gene, Toyama, Japan) and converted to cDNA using the ReverTra Ace® qPCR RT Kit (Toyobo Co., Ltd.). qPCR using the GeneAce SYBR® qPCR Mix α kit (Nippon Gene) and primers with the Thermal Cycler Dice Real Time System (Takara Bio Inc., Shiga, Japan) (Table 1). The results were a relative ratio to the control after normalization to *act-1* by the $2^{-\Delta\Delta Ct}$ method.

***Data Analysis***

Statistical analysis was performed using one sample t-test (healthspan data and *gcs-1* expression) and Kaplan-Meier followed by log-rank (Mantel-Cox). A *p*-value <0.05 was considered significant.

## Results

***UV-B Radiation Reduced Pharyngeal Pump Rate, Shortened Median Lifespan, Decreased Collagen Synthesis, and Increased Apoptosis-Related Gene Expression in C. Elegans***

Examination of healthspan with the indicator of pharyngeal pump rate per minute showed that UV-B radiation could reduce the pharyngeal pump rate per minute, both on the 7th and 12th days ($p<0.05$, Figure 1a). Additionally, the results showed that exposure to UV-B significantly shortened the median lifespan from 18 days to 13 days ($p<0.05$, Figure 1b). UV-B decreased collagen on the 7th and 12th days at mRNA expressions ($p<0.05$, Figure 1c) and protein levels ($p<0.05$, Figure 1d), suggesting that UV-B can cause damage to the cuticular layer of the worms and reduced the collagen synthesis. Next, UV-B increased the expression of *hus-1* ($p<0.05$, Figure 1e), *cep-1* ($p<0.05$, Figure 1f), egl-1 ($p<0.05$, Figure 1g), and *ced-13* ($p<0.05$, Figure 1h), indicating that UV-B induced apoptosis in *C. elegans*.

***RSV Increased Pharyngeal Pump Rate, Prolonged Lifespan, Ameliorated Collagen Depletion, and Attenuated UV-B-Induced Apoptosis in C. Elegans***

RSV increased pharyngeal pump rate at both day-7 and day-12 ($p<0.05$, Figure 2a) and prolonged lifespan of UV-B-induced worms ($p<0.05$, Figure 2b). Moreover, RSV ameliorated UV-B-induced collagen depletion on the 7th and 12th days at mRNA ($p<0.05$, Figure 2c) and protein levels ($p<0.05$, Figure 2d), suggesting that RSV protects

**Table 1. Primers used for gene expression analysis.**

| Genes | | Sequences |
|---|---|---|
| *gcs-1* | F: | 5'- TCT CTT GGA GTA CCT GGA TT -3' |
| | R: | 5'- CAA CCA TCT GGC TTC ATC GA -3' |
| *col-19* | F: | 5'- CAC ACA AAT GCT CCA CCA AC -3' |
| | R: | 5'- CTG GAT TTC CCT TCT GTC CA -3' |
| *hus-1* | F: | 5'- GGC AAT CGA CGT GTT TAT CA-3' |
| | R: | 5'- TCG TTT CGT GGA TTC ATG CC -3' |
| *cep-1* | F: | 5'- TGT CCA GAA AAT GAT AGA CG -3' |
| | R: | 5'- GCA TCG GAA ATC TTT GGC GT-3' |
| *egl-1* | F: | 5'- ACA CCC AAA ACA TTC ACA CC-3' |
| | R: | 5'- GGC AAA GGT GAG CAT CAG CA-3' |
| *ced-13* | F: | 5'- TCG AGG GCA GAA AAA CGT GA-3' |
| | R: | 5'- ACA ACA GCG GGA GAA AGT GT-3' |
| *act-1* | F: | 5'- ATG AAG ATC CTT ACC GAG CG-3' |
| | R: | 5'- TTG GCG TAC AAG TCC TTA CG -3' |

F = Forward primer; R = Reverse primer.

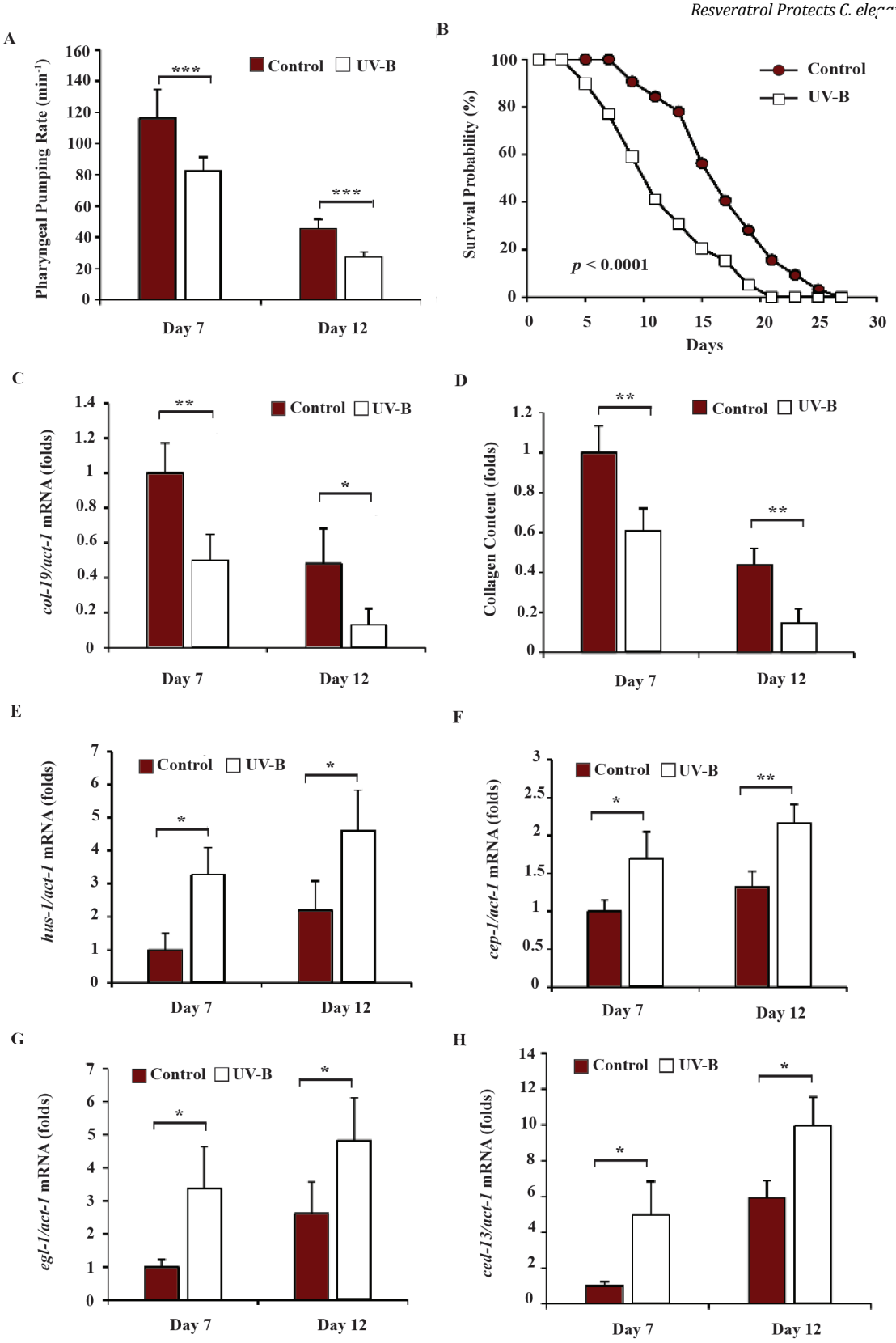


**Figure 1. UV-B radiation reduced pharyngeal pump rate, shortened median lifespan, decreased collagen synthesis, and increased apoptosis-related gene expression in** ***C. elegans*****.** UV-B radiation reduced the pharyngeal pump rate in wild-type N2 *C. elegans* on days 7 and 12 (A). UV-B exposure on day 0 shortened the lifespan, observed every 2 days (B). RT-qPCR analysis showed decreased *col-19* expression following UV-B treatment (C), and collagen content was significantly reduced after exposure to UV-B radiation (D). Apoptosis-related gene expression of *hus-1, cep-1, egl-1,* and *ced-13* was upregulated following UV-B treatment (E-H). **p*<0.05; ***p*<0.01; ****p*<0.001.

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*C. elegans* from photoaging due to UV-B radiation. Next, RSV attenuated UV-B-induced elevation on *hus-1* ($p$<0.05, Figure 2e), *cep-1* ($p$<0.05, Figure 2f), *egl-1* ($p$<0.05, Figure 2g), and *ced-13* ($p$<0.05, Figure 2h), indicating that RSV protects *C. elegans* from undergoing apoptosis.

***The Role of skn-1 in the Mechanism of Action of RSV***

The effect of RSV in preventing photoaging phenotypes due to UV-B radiation could not be observed in nematodes with skn-1 gene mutation. The pharyngeal pump rate on day 7 was not rescued by RSV treatment ($p$>0.05, Figure 3a). Pharyngeal pump rate could not be observed on day 12 because most of the nematodes had died (±90%). Observation of overall lifespan also showed similar results ($p$>0.05, Figure 3b). Moreover, the effects of RSV on UV-B-induced collagen depletion on the 7th at mRNA ($p$>0.05, Figure 3c) and protein levels ($p$>0.05, Figure 3d) showed similar trends. Next, RSV effects on the reduction of *hus-1* ($p$>0.05, Figure 3e), *cep-1* ($p$>0.05, Figure 3f), *egl-1* ($p$>0.05, Figure 3g), and *ced-13* ($p$>0.05, Figure 3h) were not observed in nematodes with *skn-1* gene mutation. Together, these results indicate that *skn-1* plays an important role as a mediator of the anti-aging effect of RSV. Furthermore, gene expression examination of *gcs-1*, the main target gene of *skn-1*, was carried out to prove that RSV activates this transcription factor. The results showed that RSV treatment at a concentration of 100 μM for 24 hours increased *gcs-1* gene expression by 2.5-fold ($p$<0.05, Figure 3i).

## Discussion

In the present study, UV-B was found to significantly reduce lifespan and healthspan, as well as causing reduction in collagen and elevation in apoptosis-related genes. The results of this study are supported by many previous studies. The entire ultraviolet spectrum (UV-A, UV-B, and UV-C) has been shown to significantly reduce the lifespan of *C. elegans*.[20] The *C. elegans* can detect UV through the LITE-1 photoreceptor and TAX-2 protein.[21] UV radiation induces aging and shortening of lifespan through oxidative stress. UV affects cellular components directly or through photosensitization mechanisms.[22] UV light can induce ROS by affecting the activity of xanthine oxidase, NADPH oxidase, and nitric oxide synthase enzymes in mitochondria.[23] UV can also cause a decrease in protein kinase C (PKC), expression which causes increased ROS production. UV radiation can modify DNA and other chromophores, resulting in increased ROS levels.[24] In addition, studies have also shown that UV radiation, through the production of hydrogen peroxide radicals, can reduce the rate of pharyngeal pumps due to stimulation of LITE-1 and GUR-3 photoreceptors.[25]

Next, this study found that RSV protects *C. elegans* from UV-B-induced photoaging phenotypes. Although RSV has been reported to extend the lifespan of some model organisms such as *Saccharomyces cerevisiae*[26] and *Drosophila melanogaster*[27], the results of this study did not show the same effect on *C. elegans*. Study showed that RSV did not increase lifespan in basal conditions, but protected *C. elegans* from juglon-induced lifespan reduction (a compound that causes oxidative stress).[12] Various report showed inconsistency, RSV caused a slight increase in lifespan in some trials but had no effect in other trials.[28] However, other researchers have shown that RSV can increase the lifespan of *C. elegans* in basal conditions.[15] RSV has direct antioxidant activity, based on the results of *in vitro* DPPH tests with an $IC_{50}$ value range of 24.5-323.9 μM,[12] so the anti-aging effect of RSV may only have an impact on pathological conditions where oxidative stress causes premature aging.[29]

In this study, UV-B exposure to *C. elegans* lead to collagen depletion at mRNA and protein levels. Collagen is essential to the flexibility and strength of human skin. However, as people age, the skin collagen likely degrades, leading to wrinkles.[30] Numerous environmental stressors, including prolonged and continuous exposure to UV-B rays, cause photoaging and seem to hasten the development of wrinkles. Even in this age of advanced medicine, rates of UV-induced skin aging remain on the rise. Nearly every sunscreen on the market provides UV-B protection.[20] To prevent UV-B-induced collagen deprivation, in this study RSV was used as treatment. RSV effectively blocked UV-B inhibitory activity on collagen. At the cellular levels, studies have demonstrated that RSV enhances collagen synthesis by activating the estrogen receptor.[31] Study discovered that the RSV-treated fibroblast exhibited reduced metalloproteinase 1 (enzymes responsible for the collagen degradation in extracellular matrix) activity than the control group.[32] Furthermore, resveratrol inhibits the expression of AP-1 and NF-kB transcription factors, which limits skin inflammation and the breakdown of collagen and elastin.[33]

Under specific circumstances, apoptosis is regulated by intrinsic genes to preserve homeostasis. Through a variety of intricate mechanisms, such as direct DNA destruction, elevated p53 levels, and activation of cell death receptors,

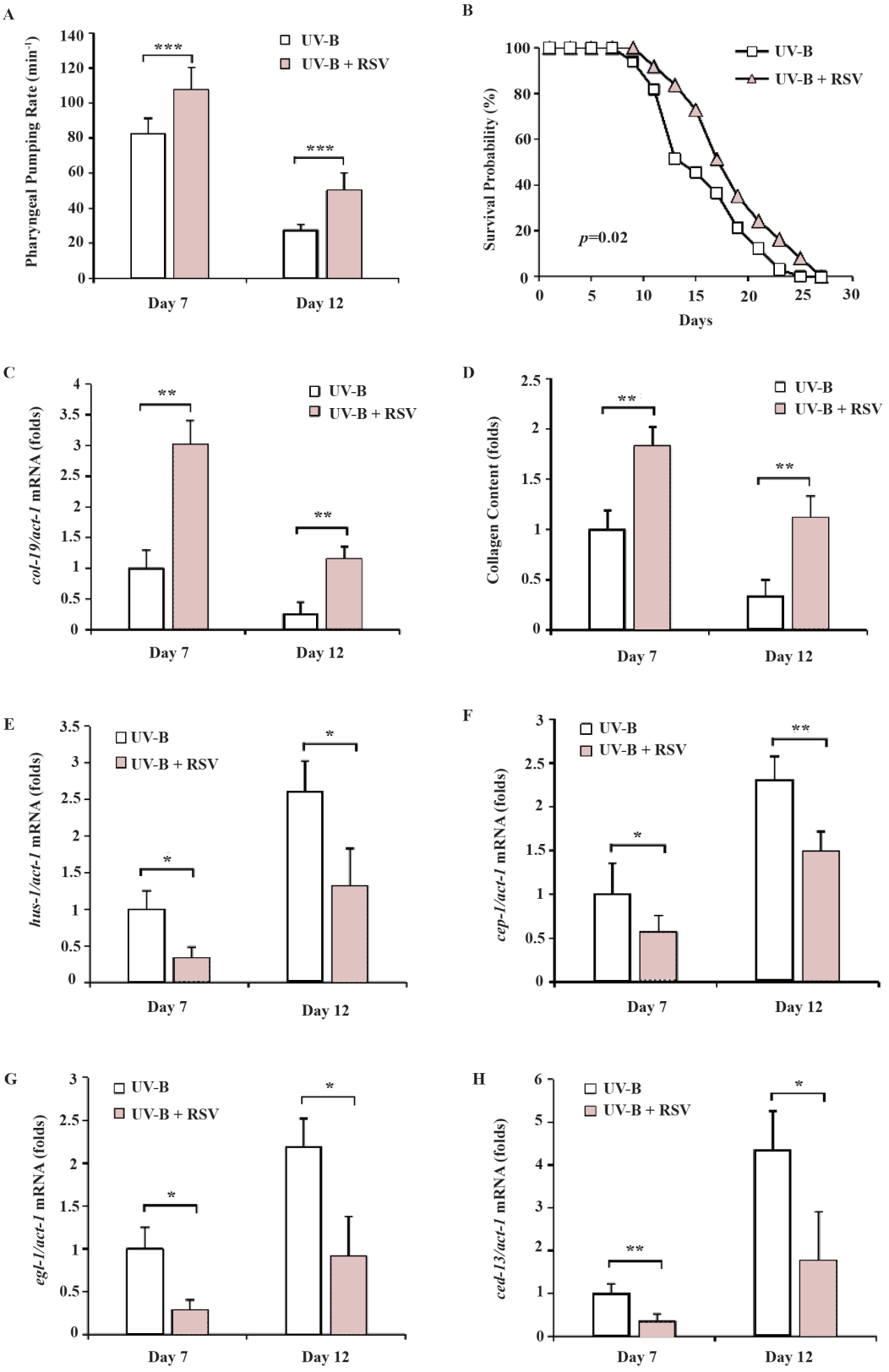


**Figure 2. RSV increased pharyngeal pump rate, prolonged lifespan, ameliorated collagen depletion, and attenuated UV-B-induced apoptosis in *C. elegans*.** RSV (100 μM) treatment increased the pharyngeal pump rate in wild-type N2 *C. elegans* exposed to UV-B on days 7 and 12 (A), and prolonged lifespan (B). RT-qPCR analysis revealed that RSV treatment restored *col-19* expression following UV-B exposure (C), while collagen content was improved in RSV-treated worms after UV-B exposure (D). RSV treatment also attenuated UV-B-induced expression of apoptosis-related genes *hus-1, cep-1, egl-1,* and *ced-13* (E-H). *$p$<0.05; **$p$<0.01; ***$p$<0.001.

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UV-B induces apoptosis.[34] In the present study, it is demonstrated that RSV increased the *C. elegans* tolerance to UV-B-induced apoptosis by examining the apoptosis-related gene expression in RT-qPCR data. Pro-apoptotic genes *egl-1* and *ced-13* exhibit up-regulated expression levels following UV-B treatment. The mechanism of BH3 domain proteins in *C. elegans* is comparable to that of humans during this canonical apoptosis activation phase.[35] Consequently, *cep-1* must orchestrate the apoptotic response of *egl-1* and *ced-13* following UV-B, and the checkpoint protein *hus-1* is also necessary for *cep-1* activation.[36] According to RT-qPCR data, RSV considerably limited the rise in *hus-1*, *cep-1*, *egl-1*, and *ced-13* expression levels brought on by UV-B, which clarified the mechanism by which RSV inhibits apoptosis.

Many studies have shown that supplementation of compounds with antioxidant activity alone has no effect on lifespan, or even has a negative effect.[37] Therefore, research is needed to prove whether RSV can also activate cellular antioxidant responses. RSV has been shown to increase the lifespan of *C. elegans* through the Sirtuin pathway and ERK.[14,15] To date, there has been no research linking RSV anti-aging activity with cellular antioxidant activity and response, so research was conducted to study the role of the *skn-1* transcription factor, which plays an important role in the oxidative stress response in *C. elegans*.

Based on studies in *C. elegans*, there are several molecular pathways involved in the regulation of the aging process. These factors include *daf-16, sir-2.1, foxa, skn-1, daf-12,* and *tor*.[38] Previously, studies showed that RSV requires *sir-2.1*, but not *daf-16*, for anti-aging effects.[15] Other studies have demonstrated the important role of MPK-1/ERK in the mechanism of action of RSV.[14] Although there have been many studies proving that RSV activates Nrf2 in various types of human cells,[9] to date there has been no study directly proving the role of *skn-1* in *C. elegans*. This study, for the first time, demonstrates that the anti-aging effects of RSV under UV-B are mediated by *skn-1*.

In this study, it was demonstrated that RSV can activate *skn-1*, as evidenced by increased expression of the gcs-1 gene. Additionally, the beneficial effects of RSV on protection towards UV-B-induced photoaging required *skn-1*. The RSV effects were completely abolished in nematode harboring loss-of-function mutation in *skn-1* gene. The mechanism of action of RSV in activating *skn-1* can be explained through at least two mechanisms. First, RSV activates MPK-1, which then induces phosphorylation of *skn-1* at residues Ser-74 and Ser-340, thereby triggering translocation of *skn-1* to the nucleus to activate antioxidant genes.[14,39] Second, based on in silico studies, RSV can bind directly to *skn-1* (binding affinity -7.313 kcal/mol), thereby activating *skn-1* with a mechanism that is still unclear.[40]

Comparing *C. elegans* to other animal models, it still has several limitations. First off, some anatomical features are absent in *C. elegans*, such as the blood-brain barrier, first-pass metabolism in the liver, blood filtration in the kidney, and blood transport system. These features may have particular impact on RSV's mechanism of action. Another drawback of *C. elegans* as a model system to forecast human research outcomes is its absence of DNA methylation, an important epigenetic tag that are altered by aging. Furthermore, it is not suitable for researching the pertinent mechanism in other animal species due to the absence of long-range transcriptional regulation. To this end, the further research using other mammals as animal models (*e.g.*, mice, rats, guinea pigs, *etc*.) is required. Additionally, observational study in humans with high consumption of RSV-containing foods could also been done to provide the clinical significance of RSV on humans aging.

## Conclusion

RSV has a protective effects on UV-B-induced aging phenotypes, including lifespan elongation, healthspan improvement, collagen protection and anti-apoptosis. This study, for the first time, proves that *skn-1* (an ortholog of Nrf2) plays an important role in the mechanism of action of RSV. These findings suggest that RSV could potentially be used as a novel anti-aging strategy.

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## Authors' Contributions

FMS performed the research concept design, data collection, data analysis, manuscript writing, and obtained research funding.

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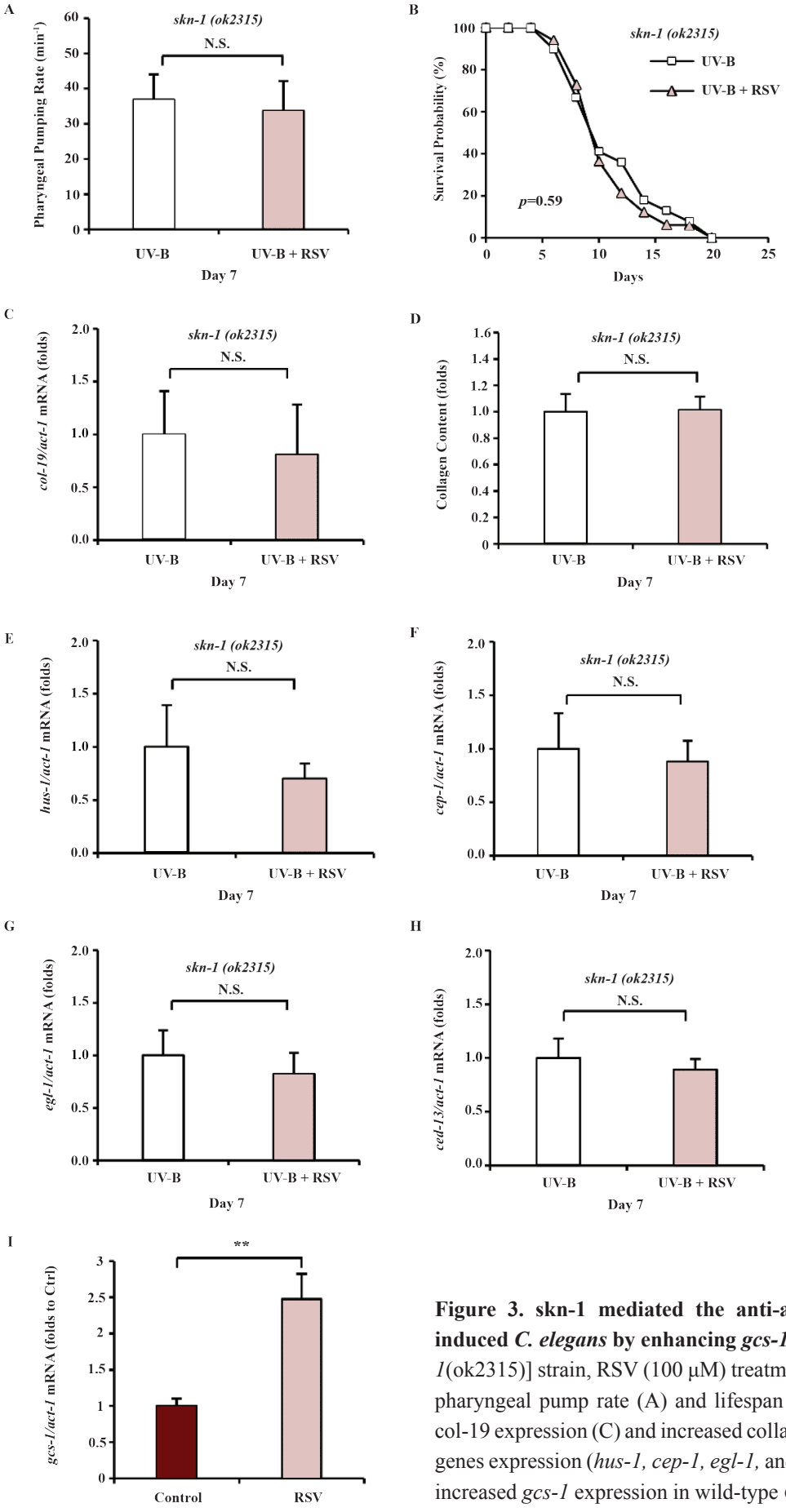


**Figure 3. skn-1 mediated the anti-aging effects of RSV in UV-B-induced *C. elegans* by enhancing *gcs-1* expression.** In the VC1772 [*skn-1*(ok2315)] strain, RSV (100 μM) treatment after UV-B exposure improved pharyngeal pump rate (A) and lifespan (B). RSV treatment also restored col-19 expression (C) and increased collagen content (D). Apoptosis-related genes expression (*hus-1, cep-1, egl-1,* and *ced-13*) was reduced (E-H). RSV increased *gcs-1* expression in wild-type *C. elegans* (I). NS: Not significant.

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