Role of insulin/insulin-like growth factor-1 signaling pathway genes on the lifespan of Caenorhabditis elegans

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ABSTRACT
Aging process is influenced by the insulin/insulin-like growth factor-1 signaling (IIS) pathway or IGF-1 signaling pathway. Studies done on the genes of this pathway were found to affect longevity. However, no conclusive results have been drawn. The purpose of this systematic review is to summarize the function of genes involved in the IIS pathway of Caenorhabditis Elegans (C. elegans), a nematode commonly used as a model organism in molecular genetics and developmental biology. A literature search for relevant studies was done through PubMed and Scopus databases using MeSH keywords Caenorhabditis elegans, C. elegans, nematode, genes, RNA, DNA, IIS pathway, IGF pathway, lifespan, and longevity. The search was limited to studies that were published in the last ten years (2008-May 2018). After exclusion of duplicates, review papers, human, in vitro, and other organismal studies, a total of 76 research articles were selected for further assessments. Data relevant to the effects of IIS genes on the lifespan of C. elegans was independently extracted. Reduction of daf-2 and age-1 and overexpression of sir-2.1 were reported to promote increment of the lifespan of C. elegans. Furthermore, differentially expressed genes that were involved in the protection against oxidative stress, pathogen attack, and toxicity include ins-18, numr-1/-2, sgk-1, and rgs-1. The knockdown of daf-2, age-1, and overexpression of sir-2.1 genes prolonged the lifespan of C. elegans while knockdown of daf-16, hsf-1, sir-2.1 as well as skn-1 shorten the lifespan of C. elegans. In conclusion, the differential expression of genes in the IIS pathway prolongs the lifespan of C. elegans.

INTRODUCTION
Countless studies have used Caenorhabditis elegans (C. elegans) as a model organism to determine the role of signaling pathways involved in aging and longevity (Chalfie et al., 1994; Feinberg et al., 2008; Boulin et al., 2006). C. elegans have been widely used as a model organism because of its 83% homologous genome to human (Lai et al., 2000). Other than that, the nematodes also have similar functions of the neurons, skin, gut, muscles, and other tissues like humans (Ahringer, 2006). C. elegans have a rapid life cycle, which is around 3 to 4 weeks. This gives an advantage for plausible observation of life stages in the aging process of the organism. Three major
Table 1: Effect of differential genes expression on the mean lifespan of *C. elegans*.

| No. | Author                  | No. of worms used | Culture conditions | Gene tested                  | Lifespan (days) |
|-----|-------------------------|-------------------|-------------------|-----------------------------|-----------------|
| 1   | (Altintas et al., 2016) | No data           | 20°C *NGM* E. coli OP50 | N2a Alg-1(gk214)b Alg-1;daf-2b Alg-1;daf-16b Alg-2(ok304)b Alg-2;daf-2b Alg-2;daf-16b Daf-2(e1370)b Daf-16(mu86)b | 16.28±2.26 12.81±2.36 11.35±1.90 19.59±1.38 38.93±0.39 11.73±0.33 43.08±3.67 12.75±1.69 |
| 2   | (Chen et al., 2018)     | 102-165           | 20°C Liquid E. coli OP50 | N2a Daf-2(e1370)b Daf-16(mu86)b Eat-2(ad1116)b Hsf-1(sy441)b Mev-1(kn-1)b Sir-2.1(ok434)b | 19.96±0.39 36.64±0.58 29.97±0.29 16.02±0.11 17.59±0.29 |

Pathways that have been shown to influence the lifespan of these nematodes are insulin/insulin-like growth factor (IIS or IGF-1), a target of rapamycin (TOR), and germline signaling pathways. Although these pathways involve different sets of transcription factors, there is partial overlapping of mechanisms involved in the aging process.

IIS pathway was the first established lifespan-regulating signaling pathway. The IIS pathway contains many conserved longevity-regulatory components that regulate aging in a DAF-16-dependent manner (Morris et al., 1996; Kimura et al., 1997). TOR is a mechanistic target of rapamycin, and a serine/threonine kinase that regulates cell growth, proliferation, motility and survival, protein synthesis, autophagy, and transcription. TOR is activated under nutrient- and energy-sufficient conditions, which in turn stimulates growth. Inhibition of TOR signaling was found to increase the lifespan of *C. elegans* in a DAF-16-dependent manner (Kapahi et al., 2010). Similar to the IIS pathway, DAF-16/FOXO is also required for the lifespan extension of germlineless animals (Arantes-Oliveira et al., 2002). Translocation of DAF-16/FOXO to the nucleus in intestinal cells promotes longevity through germline signaling (Kenyon, 2010).

Many studies have reported on the different roles of genes in the IIS pathway. The changes in expression of these genes affects the longevity of *C. elegans* differently depending on the species of nematode used and experimental conditions. The purpose of this review is to summarize the effect of IIS pathway genes to the lifespan of *C. elegans* systematically.

Materials and Methods

An electronic search of the PubMed and Scopus databases were carried out using the keywords: “Caenorhabditis elegans” OR “C. elegans” OR "nematode" AND "genes" OR "RNA" OR "DNA" AND "insulin/insulin-like pathway" OR "IIS pathway" OR "IGF pathway" AND "lifespan" AND "longevity." The search was limited to studies that were published in the last ten years (2008-May 2018). All titles and abstracts were screened after exclusion of duplicates, review papers, “human,” “in vitro” and other organismal studies and papers published in languages other than English. After the filtering process, a total of 84 research articles were used for this study. However, the full text of 8 articles were not retrievable due to unavailability, leaving only 76 articles included in this review (Figure 1). The studies were compiled for data extraction. Data relevant to the effects of IIS pathway genes on the lifespan of *C. elegans* were independently extracted (Tables 1, 2, 3, 4, 5, 6, 7 and 8).

RESULTS AND DISCUSSION

Multiple studies, along the years, have shown that lifespan expansion in *C. elegans* mostly correlated with daf-16 transcription via the IIS pathway. Single mutation of IIS genes such as daf-2, age-1, or daf-16 leads to inhibition of the IIS pathway and extension of lifespan (Uno and Nishida, 2016). In this review, most studies were found to be done on daf-2, daf-16, age-1, skn-1, hsf-1, and sir-2.1 genes, which are all
Table 2: (Continue from Table 1) Effect of differential genes expression on the mean lifespan of *C. elegans*.

| No. | Author | No. of worms used | Culture conditions | Gene tested | Lifespan (days) |
|-----|--------|-------------------|--------------------|-------------|-----------------|
| 3   | (Chaudhari and Kipreos, 2017) | No data | 20°C Liquid E. coli OP50 | N2a | 28.0 |
|     |        |                   |                    | Candid-1b | ↑35.0 |
|     |        |                   |                    | Lin-23b | ↑38.0 |
|     |        |                   |                    | Spg-7b | ↑31.0 |
|     |        |                   |                    | Candid-1;spg-7(ek25)b | ↑31.0 |
|     |        |                   |                    | Ppgn-1b | ↑34.0 |
|     |        |                   |                    | Ppgn-1;spg-7b | ↑41.0 |
|     |        |                   |                    | Eat-3b | No effect |
|     |        |                   |                    | Daf-2(e1370)b | ↑70.0 |
|     |        |                   |                    | Daf-2;eat-3b | ↑41.0 |
|     |        |                   |                    | Fzo-1b | ↓22.0 |
|     |        |                   |                    | Daf-16(mu86)b | ↓25.0 |
|     |        |                   |                    | Eat-2(ad1116)b | ↑40.0 |
|     |        |                   |                    | Eat-2;eat-3b | ↓21.0 |
|     |        |                   |                    | Glp-1b | ↑45.0 |
|     |        |                   |                    | Glp-1;eat-3b | No effect |
| 4   | (Wu et al., 2017) | 30 | 25°C NGM E. coli OP50 | N2a | 15.8±2.5 |
|     |        |                   |                    | Age-1(nr2017)b | ↑18.8±2.8 |
|     |        |                   |                    | Age-1(hx546)b | ↑32.1±8.9 |
|     |        |                   |                    | Age-1;rgs-1b | ↑32.8±8.0 |
|     |        |                   |                    | Daf-16(mu86)b | ↓6.6±0.7 |
|     |        |                   |                    | Daf-16;rgs-1b | ↓6.5±0.8 |
| 5   | (Zhao et al., 2017) | 50 | 20°C NGM E. coli OP50 | N2a | 18.90±0.24 |
|     |        |                   |                    | Age-1(hx546)b | ↑32.62±0.08 |
|     |        |                   |                    | Daf-2(e1370)b | ↑29.79±0.14 |
|     |        |                   |                    | Daf-16(mgd50)b | ↓16.73±0.20 |
|     |        |                   |                    | Sir-1(zu169)b | ↓18.32±0.26 |
|     |        |                   |                    | Sir-2.1(ok434)b | ↓13.90±0.06 |
| 6   | (Mack et al., 2017) | 40 | 20°C NGM E. coli OP50 | N2a | 20.56±0.4 |
|     |        |                   |                    | Daf-2b | ↑49.40±1.2 |
|     |        |                   |                    | Mbk-1(pk1389)b | ↓19.21±0.28 |
|     |        |                   |                    | Hpk-1(pk1393)b | ↓15.37±0.28 |
| 7   | (Kumar et al., 2016) | 30-40 | 20°C NGM E. coli OP50 | N2a | 15.9±5.0 |
|     |        |                   |                    | Eat-2(ad1116)b | ↑17.9±5.1 |
|     |        |                   |                    | isp-1(qm150)b | ↑20.0±6.4 |
|     |        |                   |                    | Sir-2.1(ok434)c | ↑17.0±3.7 |
|     |        |                   |                    | Daf-16(mu86)b | ↓12.6±3.5 |
|     |        |                   |                    | Daf-2(e1370)b | ↓35.4±8.9 |
|     |        |                   |                    | Rrf-3(pk1426)b | ↓15.7±4.0 |
|     |        |                   |                    | Rict-1(mg360)b | ↓12.1±2.6 |
|     |        |                   |                    | Hsf-1(sy441)b | ↓11.5±1.9 |
|     |        |                   |                    | Age-1(hx546)b | ↑20.7±6.4 |
|     |        |                   |                    | Age-1(am88)b | ↑22.9±6.2 |

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| Table 2 continued |
|-------------------|
| 8 (Akhoon et al., 2016) |
| 20°C | 50 | N2a | 13.7±0.4 |
| *NGM | E. coli | OP50 | N2a | 13.7±0.4 |
| *NGM | E. coli | Mev-1(kn1)b | 9.15±0.3 |
| Sgk-1(ok538)b | 17.06±0.5 |
| Daf-16(mgDf50)b | 11.09±0.3 |
| Skn-1(zu67)b | 11.69±0.3 |
| Hsf-1(sy441)b | 10.20±0.25 |

| 9 (Zamberlan et al., 2016) |
| 20°C | 90 | N2a | 12±1.15 |
| *NGM | E. coli | OP50 | N2a | 12±1.15 |
| *NGM | E. coli | Daf-2b | 22±1.75 |
| Daf-16b | 10±0.57 |
| Hsf-1b | 8±1.15 |
| Skn-1b | 9±0.86 |

| 10 (Khanna et al., 2016) |
| 21.5°C | 60 | N2a | 13.9±0.4 |
| *NGM | E. coli K-12 | OP50 | N2a | 13.9±0.4 |
| Daf-2(e1370)b | 26.4±0.9 |
| Daf-16(mu86)b | No numerical data |
| Daf-16;daf-2b | 12.7±0.3 |
| Age-1(hx546)b | 12.6±0.4 |
| Sir-2.1(ok434)b | 17.1±0.5 |
| Mek-1(ks54)b | 17.4±0.5 |
| Skn-1(zu67)b | 12.1±0.4 |
| Daf-2(el368)b | 10.9±0.3 |

| 11 (Im et al., 2016) |
| 15°C | 40-50 | N2a | 14.2±0.3 |
| *NGM-Lite | E. coli | OP50 | N2a | 14.2±0.3 |
| Daf-2(e1370)b | 26.4±0.9 |
| Skn-1(zu67)b | No numerical data |
| Daf-16(mu86)b | 12.7±0.3 |
| Daf-16;daf-2b | 12.6±0.4 |
| Mek-1(ks54)b | 17.1±0.5 |
| Daf-2(el368)b | 17.4±0.5 |
| Age-1(hx546)b | 12.1±0.4 |
| Sir-2.1(ok434)b | 10.9±0.3 |

| 12 (Oláhová and Veal, 2015) |
| 15°C | 15 | N2a | 24.74±0.55 |
| *NGM-Lite | E. coli | OP50 | N2a | 24.74±0.55 |
| Daf-2(e1370)b | 32.31±0.65 |
| Skg-1(gf15)b | 21.83±1.01 |
| Hsf-1b | 22.72±1.07 |

| 13 (Mizunuma et al., 2014) |
| 23°C | 100 | N2a | 14.4±0.1 |
| *NGM | E. coli HT115(DE3) | OP50 | N2a | 14.4±0.1 |
| Shc-1(ok198)b | 38%(8.9±0.1) |
| Shc-1(ok198)c | 42% |
| Daf-16(mu86)b | 15.4±0.4 |
| Shc-1;daf-16b | 10.8±0.3 |
| Shc-1;fer-15(b26)b | 10.5±0.2 |
| Fer-15b | 14.0±0.2 |
| Daf-16(mgDf50);fer-15b | 10.1±0.2 |
| Daf-16 shc-1;fer-15b | 10.2±0.3 |
| Jnk-1(gk7)b | 11.6±0.2 |
| Shc-1;Jnk-1b | 10.9±0.1 |

| 14 (Bansal et al., 2015) |
| 20°C | 120 | N2a | 20.0±0 |
| *NGM | E. coli OP50 | N2a | 20.0±0 |
| Daf-2(e1370)b | 43.0±0 |
| Ife-2(ok306)b | 29.0±0.14 |
| Clk-1(qm30)b | 25.0±0 |
| Eat-2(ad1113)b | 26.5±2.1 |

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| No. | (Author et al., Year) | Temperature | Media | Strain 1 | Strain 2 | Strain 3 | Strain 4 | Strain 5 | Strain 6 |
|-----|-----------------------|-------------|-------|----------|----------|----------|----------|----------|----------|
| 15  | (Rathor et al., 2015) | 20°C        | N2a   | Mev-1(kn-1)b | Daf-16(mgf50)b | Sir-2.1(ok434)c | Skn-1(zu135)b | Eat-2(ad1116)b | 16.56±0.26 |
|     |                       |             |       |           |          |          |          |          | ↓12.42±0.3 |
|     |                       |             |       |           |          |          |          |          | ↑14.19±0.07 |
| 16  | (Horikawa et al., 2015) | 15°C       | N2a   | Daf-41(ok3052)b | Daf-2(e1370)b | Pges-2(ok3316)b | Gst-4&msp-38(ok2358)b | 30.6±0.13 |
|     |                       |             |       |           |          |          |          |          | 150 ± 0.8  |
|     |                       |             |       |           |          |          |          |          | 20°C      |
|     |                       |             |       |           |          |          |          |          | 22.6 ± 0.4 |
|     |                       |             |       |           |          |          |          |          | ↓20.9±0.4  |
|     |                       |             |       |           |          |          |          |          | ↑23.3±0.0  |
|     |                       |             |       |           |          |          |          |          | ↑41.5±0.7  |
|     |                       |             |       |           |          |          |          |          | ↓20.1±0.3  |
|     |                       |             |       |           |          |          |          |          | ↑23.6±0.5  |
| 17  | (Seo et al., 2015)    | 20°C        | N2a   | Hel-1(gk148684)b | Daf-2(e1370)b | Hel-1:osm-5(p813)b | Vhl-(ok161)b | Hel-1:eat-2b | 16.9±0.6  |
|     |                       |             |       |           |          |          |          |          | ↑17.0±0.4  |
|     |                       |             |       |           |          |          |          |          | ↑39.7±1.1  |
|     |                       |             |       |           |          |          |          |          | ↑27.0±0.9  |
| 18  | (Golegaonkar et al., 2015) | 20°C    | N2a   | Daf-18(E1375)b | Akt-1(Mg144)b | Jnk-1(Gk7)b | Jkk-1(Km2)b | Daf-16(mgDf50)b | 22.78±0.23 |
|     |                       |             |       |           |          |          |          |          | 22.78±0.23 |
|     |                       |             |       |           |          |          |          |          | ↓18.60±0.26 |
|     |                       |             |       |           |          |          |          |          | ↓18.55±0.26 |
|     |                       |             |       |           |          |          |          |          | ↑39.52±0.61 |
|     |                       |             |       |           |          |          |          |          | ↑33.38±0.43 |
|     |                       |             |       |           |          |          |          |          | ↑29.18±0.40 |
|     |                       |             |       |           |          |          |          |          | ↑17.80±0.25 |
|     |                       |             |       |           |          |          |          |          | No effect |
|     |                       |             |       |           |          |          |          |          | (22.78±0.23) |
| 19  | (Ewald et al., 2015)  | 20°C        | N2a   | Skn-1(zu67)b | Daf-2(e1370)b | GST-2(ad1111)b | Daf-2;skn-1b | 23.4±0.3  |
|     |                       |             |       |           |          |          |          |          | ↓16.9±0.2 |
|     |                       |             |       |           |          |          |          |          | ↑36.7±0.5  |
|     |                       |             |       |           |          |          |          |          | ↓17.1±0.2 |

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| # | (Author, Year) | Temperature | E. coli | Gene Interaction | Value ± SD | Note |
|---|---|---|---|---|---|---|
| 20 | (Zheng et al., 2014) | 20°C | *NGM | Daf-16(mu86)b Ins-7(ok1573)c | 17.04±0.42 | 15.72±0.26 |
|   |   |   | E. coli OP50 |   | 19.08±0.29 |   |
| 21 | (Kim et al., 2014) | 20°C | *NGM | Daf-2b Daf-16(mu86)b Nog-1b Nog-1;daf-2b Nog-1;daf-16b Nog-1;daf-2b Nog-1;daf-16b Nog-1;daf-2b | 12.21±0.24 | 13.2±0.30 |
|   |   |   | E. coli OP50 |   | 12.9±0.25 |   |
| 22 | (Breibning et al., 2014) | 20°C | *NGM | Daf-16(mu86)b Daf-16;daf-2b Nog-1b Nog-1;daf-2b Nog-1;daf-16b Nog-1;daf-2b Nog-1;daf-16b Nog-1;daf-2b Nog-1;daf-16b Nog-1;daf-2b Nog-1;daf-16b Nog-1;daf-2b | 17.0±1.0 | 29.0±2.0 |
|   |   |   | E. coli OP50 |   | 30.0 |   |
| 23 | (Ferguson et al., 2013) | 20°C | E. coli | Tatn-1(baf1)b Eak-7(3188)b Eak-7;tatn-1b Eak-2(gt33)b Tatn-1;ak-2b | 21.0 | 14.0 |
|   |   |   | HB101 NGM-streptomycin |   | 13.0 |   |

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| Table 2 continued |
|--------------------|
| 20°C | N2a | 22.0 |
| E. coli | Tatn-1b | ↑24.0 |
| HT115 | Daf-2(e1368)b | ↑30.5 |
| NGM-streptomycin | Tatn-1;daf-2b | ↑37.0 |
| Daf-16(mgDf47)b | ↓14.5 |
| Tatn-1;daf-16b | ↓17.0 |
| **20°C** | **N2a** | **14.23±1.81** |
| *NGM | Daf-2(e1368)b | ↑28.24±5.39 |
| E. coli | Daf-12b | ↓13.86±1.84 |
| OP50 | Daf-12;daf-2b | ↑25.26±3.95 |
| Daf-2(e1370)b | ↑32.34±11.39 |
| Daf-2;daf-12b | ↑31.77±9.86 |
| Daf-36b | ↓13.13±1.60 |
| Daf-36;daf-2b | ↑22.84±4.94 |
| Daf-9b | ↓13.24±1.79 |
| Daf-9;daf-2b | ↑24.96±4.67 |
| **20°C** | **N2a** | **15.07±2.74** |
| *NGM | Daf-2(e1368)b | ↑24.93±4.37 |
| E. coli | Daf-12b | ↓13.77±2.26 |
| HT115 | Daf-12;daf-2b | ↑24.61±5.81 |
| Daf-2(e1370)b | ↑27.60±8.85 |
| Daf-2;daf-12b | ↑25.23±9.17 |
| Daf-36b | ↓9.58±2.54 |
| Daf-36;daf-2b | ↑23.70±5.45 |
| Daf-9b | ↓11.80±2.32 |
| Daf-9;daf-2b | ↑23.99±5.52 |
| 24 (Dumas et al., 2013) | 60 |
| 25 (Wan et al., 2013) | 60 |
| 26 (Guha et al., 2013) | 30 |
| 27 (Lin et al., 2011) | 50 |
| 20°C | N2a | 17.0 |
| N2a | 11.83±0.94 |
| Daf-2(e1370)b | ↑65.0 |
| Daf-12b | ↑21.0 |
| Eat-2(mu86)b | ▼31.0 |
| Daf-2(e1370)b | ↑26.66±1.7 |
| Eat-2(d11116)b | ↑28.50±1.3 |
| Daf-16(mgDf50)b | ↓8.66±1.1 |
| Daf-2(e1370)b | ↑28.50±1.3 |
| Daf-2(e1370)b | ▼10.50±0.8 |
| Age-1(hx546)b | ↑14.00±1.0 |
| Osr-1(rm1)b | ▼12.50±0.0 |
| Unc-43(n1186)b | ↑10.78±0.0 |
| Sek-1(ag1)b | ↑13.00±1.9 |
| Jnk-1(gk7)b | | |
| Sir-2.1(ok434)c | | |
| Par-4(it47)Vb | | |
| 20°C | N2a | 15.3±0.58 |
| N2a | 15.3±0.58 |
| Daf-3(ok1744)b | ↑14% (17.4±0.69) |
| Daf-1b | ↑12% (22.0±0.52) |
| Daf-2b | ↑10% (21.6±0.57) |
| Asm-3(ok1744)b | ↑14% (17.4±0.69) |
| Asm-1b | ↑12% (22.0±0.52) |
| Asm-2b | ↑10% (21.6±0.57) |
| Asm-3;apf-1b | ↑21% (51.3±2.23) |
| Asm-3;age-1b | ↑67% (69.6±1.52) |
| Age-1(mg305)b | ↑41.7±0.98 |
| Aap-1(m889)b | ↑42.4±1.79 |

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Table 2 continued

| No. | Study (Reference Year) | Temperature (°C) | Treatment | Phenotypes | Effect | Effect | Effect | Effect |
|-----|------------------------|------------------|-----------|------------|--------|--------|--------|--------|
| 28  | (Matsunaga et al., 2012) | 25°C             | N2a       | *NGM       | Ins-18(tm339)c | 17.0   | by 3.1 | by 2.7 | by 4.8 |
|     |                        |                  |           | E. coli    | Ins-18(tm339)b | No numerical data |
|     |                        |                  |           | OP50       | Ins-18;ins-7(tm1907)b | ↓by 7.0 |
|     |                        |                  |           |            | Daf-2;ins-18b | ↑by 7.0 |
|     |                        |                  |           |            | Daf-2(e1370)b | ↑by 9.0 |
| 29  | (Vaccaro et al., 2012)  | 20°C             | N2a       | *NGM       | Daf-2(e1370)b | 16.0   | by 3.8 | by 1.3 | by 4.8 |
|     |                        |                  |           | E. coli    | Daf-2(e1370)b | No numerical data |
|     |                        |                  |           | OP50       | Tdp-1(ok803)b | ↑by 2.0 |
|     |                        |                  |           |            | Daf-2;tdp-1b | ↑by 3.0 |
|     |                        |                  |           |            | Daf-16;tdp-1b | ↓by 1.2 |
| 30  | (Grompone et al., 2012) | No data         | N2a       | *NGM       | Daf-16b | 24.0   | by 4.0 | by 1.0 | by 5.0 |
|     |                        |                  |           | E. coli    | Daf-16b | No numerical data |
|     |                        |                  |           | OP50       | Skn-1b | by 4.0 |
| 31  | (Barna et al., 2012)    | 20-30            | N2a       | *NGM       | Hsf-1(sy441)b | 20.0   | by 3.0 | by 1.3 |
|     |                        |                  |           | E. coli    | Hsf-1(sy441)b | No numerical data |
|     |                        |                  |           | OP50       | Daf-7b | by 3.0 |
| 32  | (Hahm et al., 2011)     | 45-60            | N2a       | *NGM       | Gpa-9(pk438)b | 19.56±0.62 | by 20.26±1.09 |
|     |                        |                  |           | E. coli    | Gpa-9(pk438)b | No effect |
|     |                        |                  |           | OP50       | Gpa-9(pk438)b | (19.56±0.62) |
|     |                        |                  |           | (OD=0.18)  | Gpa-9(XSc) | No effect |
|     |                        |                  |           | High Density Feeding (HDF) | Gpa-9(XSc) | (16.22±0.14) |
|     |                        |                  |           | E. coli    | Gpa-9(pk438)b | ↑by 20.08±0.18 |
| 33  | (Huang et al., 2011)    | 100              | N2a       | *NGM       | Daf-2b | 17.3±0.4 | by 29.1±1.4 |
|     |                        |                  |           | E. coli    | Daf-2b | by 20.1±0.7 |
|     |                        |                  |           | OP50       | Daf-2b | ↑by 36.7±1.7 |
|     |                        |                  |           |            | Daf-16;sea-2;daf-2b | ↓by 13.1±0.5 |
| 34  | (Cornils et al., 2011)  | 100              | N2a       | *NGM       | Ins-6(tm2416)b | 13.0±0.1 |
|     |                        |                  |           | E. coli    | Daf-28(tm2308)b | ↑by 14.5±0.3 |
|     |                        |                  |           | OP50       | Daf-28(tm2308)b | ↑by 13.9±0.2 |
|     |                        |                  |           |            | Ins-1(nr2091)b | ↓by 12.6±0.3 |
|     |                        |                  |           |            | Ins-6;daf-28b | ↑by 13.9±0.4 |

Continued on next page
|   | (Kühlbrodt et al., 2011) | 25-50 | 20°C | N2a  | 26.0 |
|---|------------------------|-------|------|------|------|
| 35 | *NGM E. coli OP50       |       |      | Atx-3(gk193)b | ↑30.0 |
|   |                        |       |      | Daf-2(e1370)b | ↑40.0 |
|   |                        |       |      | Cdc-48.2(tm659)b | ↑28.0 |
|   |                        |       |      | Cdc-48.2;atx-3b | ↑28.0 |
|   |                        |       |      | Cdc-48.1(tm544)b | ↑30.0 |
|   |                        |       |      | Cdc-48.1;atx-3b | ↑43.0 |
|   |                        |       |      | Cdc-48.1;daf-2;atx-3b | ↑40.0 |
|   |                        |       |      | Daf-16b | ↓20.0 |
|   |                        |       |      | Cdc-48.1;atx-3;daf-16b | ↓18.0 |
|   |                        |       |      | Pha-4b | ↑27.0 |
|   |                        |       |      | Cdc-48.1;atx-3;pha-4b | ↑35.0 |
|   | (Yazaki et al., 2011)  | 100   | 20°C | N2a  | 31.5±6.4 |
| 36 | *NGM E. coli OP50       |       |      | Age-1(hx546)b | ↑47.1±15.1 |
|   |                        |       |      | Daf-16(mgdf50)b | ↓19.2±2.8 |
|   | (Henis-Korenblit et al., 2010) | 46 | 20°C | N2a  | 16.5 |
|   | *NGM E. coli OP50       |       |      | Daf-2(e1370)b | ↑42.0 |
|   |                        |       |      | Ire-1(ok799);daf-2b | ↑19.9 |
|   |                        |       |      | Daf-2(e1368)b | ↑32.8 |
|   |                        |       |      | Daf-2;xbp-1b | ↑23.6 |
|   |                        |       |      | Ire-1(ok799);daf-2b | ↓16.0 |
|   |                        |       |      | Ire-1(ok799)b | ↓13.2 |
|   |                        |       |      | Daf-2;xbp-1b | ↑36.6 |
|   |                        |       |      | Xbp-1(zc12)b | ↓16.2 |
|   | (Hashimoto et al., 2010) | 15 | 20°C | N2a  | 34.0 |
| 38 | *NGM E. coli OP50       |       |      | Eat-2(ad1116)b | ↑44.0 |
|   |                        |       |      | Daf-16(mgDf50)b | ↓24.0 |
|   | (Thyagarajan et al., 2010) | 60 | 20°C | N2a  | 13.36±0.6 |
| 39 | *NGM E. coli OP50       |       |      | Ets-4(ok165)b | ↑18.0±0.4 |
|   |                        |       |      | Ets-4(uz1)b | ↑18.2±0.4 |
|   |                        |       |      | Daf-2b | ↑22.4±1.4 |
|   | (Shen et al., 2010b)    | 30 | 20°C | N2a  | 13.1±0.3 |
| 40 | *NGM E. coli OP50       |       |      | Daf-16(mu86)b | ↓10.7±0.7 |
|   |                        |       |      | Daf-2(e1370)b | ↑30.6±1.6 |
|   |                        |       |      | Ttx-3(ks5)b | ↓11.8±0.4 |
|   |                        |       |      | Sra-11(ok630)b | ↓13.0±0.5 |
|   |                        |       |      | Ceh-10(ct78)b | ↓7.9±0.5 |
|   |                        |       |      | Ceh-23(ms23)b | ↓12.8±0.4 |
|   | (Shen et al., 2010a)    | 30 | 20°C | N2a  | 13.1±0.3 |
| 41 | *NGM E. coli OP50       |       |      | Daf-16(mu86)b | ↓10.7±0.7 |
|   |                        |       |      | Daf-2(e1370)b | ↑30.6±1.6 |
|   |                        |       |      | Odr-7(ky4)b | ↑16.6±0.6 |
|   |                        |       |      | Odr-2(n2145)b | ↑16.3±0.6 |
|   |                        |       |      | Odr-3(n2150)b | ↑16.6±0.6 |
|   | (Chuang et al., 2009)   | 60 | 20°C | N2a  | 24.0 |
| 42 | *NGM E. coli OP50       |       |      | Tir-1b | ↑18% |
|   |                        |       |      | Daf-16b | ↓25% |
| Table 2 continued |
|-------------------|
| 43    | (Hahm et al., 2009) | 100 | 20°C | N2a | 22.0 |
|       | *NGM                   |     |      | Gpa-3(pk35)b | ↓20.0 |
|       | E. coli                |     |      | Gpa-3(syls25)b | ↑35.0 |
|       | OP50                   |     |      | Daf-11(m47)b | ↑25.0 |
|       |                        |     |      | N2a | 16.5 |
|       | *NGM                   |     |      | Ced-3(n717)b | ↓15.6 |
|       | E. coli                |     |      | Daf-2b | ↑30.1 |
| 44    | (Jia et al., 2009)    | No data | 20°C | N2a | 20.84±4.71 |
|       | *NGM                   |     |      | Eat-2(ad1113)b | ↑25.90±4.51 |
|       | E. coli                |     |      | Daf-2(e1370)b | ↑48.36±12.70 |
|       | OP50                   |     |      | Daf-16(m26)b | ↓12.84±2.11 |
| 45    | (Zhang et al., 2009)  | 10 | 20°C | N2a | 12.7±2.1 |
|       | liquid                 |     |      | Eat-2(ad1113)b | ↑23.5±2.7 |
|       | E. coli                |     |      | Daf-2(e1370)b | ↑13.7±2.6 |
|       | OP50                   |     |      | Daf-2(e1370)b | ↑12.9±1.9 |
|       |                        |     |      | Sdf-9(ut187)b | ↑12.9±2.0 |
|       |                        |     |      | Sdf-9(mg337)b | ↑12.9±1.9 |
|       |                        |     |      | Eak-3(mg329)b | ↑12.9±1.6 |
|       |                        |     |      | Eak-3(mg344)b | ↓12.6±2.6 |
|       |                        |     |      | Eak-4(mg348)b | ↑12.9±1.9 |
|       |                        |     |      | Akt-1(mg306)b | ↑13.0±2.1 |
|       |                        |     |      | Akt-1(mg306)b | ↑13.1±2.2 |
|       |                        |     |      | Akt-1;sd-9(ut187)b | ↑12.7±2.5 |
|       |                        |     |      | Akt-1;sd-9(mg337)b | ↑13.0±2.5 |
|       |                        |     |      | Sdf-9(ut187)b | ↑12.9±2.0 |
|       |                        |     |      | Sdf-9(mg337)b | ↑12.9±1.9 |
|       |                        |     |      | Eak-6(mg329)b | ↑12.9±1.6 |
|       |                        |     |      | Eak-6(mg329)b | ↑12.9±1.6 |
|       |                        |     |      | Eak-6(mg344)b | ↑12.9±1.6 |
|       |                        |     |      | Eak-6(mg344)b | ↑12.9±1.6 |
| 46    | (Zhang et al., 2008)  | 101 | 20°C | N2a | 32.1±4.2 |
|       | *NGM                   |     |      | Age-1(hx546)b | ↑37.4±5.5 |
|       | E. coli                |     |      | Daf-16(mgDf50)b | ↓18.6±0.5 |
|       | OP50                   |     |      | Sod-2;daf-2 | ↑24±0.7 |
|       |                        |     |      | Mev-1(kn1)b | ↑21.8±2.1 |
|       |                        |     |      | Eak-3(mg344)b | ↑12.6±2.6 |
|       |                        |     |      | Eak-4(mg348)b | ↑12.9±1.9 |
|       |                        |     |      | Akt-1(mg306)b | ↑13.0±2.1 |
|       |                        |     |      | Akt-1(mg306)b | ↑13.1±2.2 |
|       |                        |     |      | Akt-1;sd-9(ut187)b | ↑12.7±2.5 |
|       |                        |     |      | Akt-1;sd-9(mg337)b | ↑13.0±2.5 |
|       |                        |     |      | Sod-2;daf-2 | ↑24±0.7 |
|       |                        |     |      | Sod-3;daf-2 | ↑24±0.7 |
|       |                        |     |      | Sod-2;daf-2 | ↑24±0.7 |
|       |                        |     |      | Sod-3;daf-2 | ↑24±0.7 |
|       |                        |     |      | Sod-2;daf-2 | ↑24±0.7 |
| 47    | (Banfield et al., 2008) | 100 | 20°C | N2a | 20.0 |
|       | *NGM                   |     |      | Age-1(hx546)b | ↑37.4±5.5 |
|       | E. coli                |     |      | Daf-16(mgDf50)b | ↓18.6±0.5 |
|       | OP50                   |     |      | Sod-2;daf-2 | ↑24±0.7 |
|       |                        |     |      | Mev-1(kn1)b | ↑21.8±2.1 |
| 48    | (Honda et al., 2008)  | No data | 25°C | N2a | 15.0 |
|       | *NGM                   |     |      | Pcm-1(qa201)b | ↑17±0.4 |
|       | E. coli                |     |      | Daf-2(m41)b | ↑24±0.7 |
|       | OP50                   |     |      | Daf-2(m41)b | ↑24±0.7 |
|       |                        |     |      | Daf-2(m41)b | ↑24±0.7 |
|       |                        |     |      | Daf-2(m41)b | ↑24±0.7 |
| 49    | (Honda et al., 2008)  | No data | 15°C | N2a | 30.0 |
|       | *NGM                   |     |      | Sod-2(sj173)b | ↓22.5±1.4 |
|       | E. coli                |     |      | Sod-3(sj134)b | ↓21.5±1.1 |
|       | OP50                   |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
|       |                        |     |      | Sod-2;sd-3b | ↓20.4±2.3 |
Table 3: *(Continue from Table 2)* Effect of differential genes expression on the mean lifespan of *C. elegans.*

| No.  | Author            | No. of worms used | Culture conditions | Gene tested                  | Lifespan (days)  |
|------|-------------------|-------------------|--------------------|-------------------------------|------------------|
| 49(Continue) | *(Honda et al., 2008)* | No data | 15°C | Daf-2; sod-3<sup>c</sup> | $\uparrow 56.3 \pm 2.3$ |
|      |                   |                   | *NGM               | Daf-2; mev-1<sup>b</sup>     | $\uparrow 46.1 \pm 0.3$ |
|      |                   |                   | E. coli OP50        | Daf-7; sod-3<sup>b</sup>     | $\uparrow 23.2 \pm 3.9$ |
|      |                   |                   |                    | Sod-2; daf-7; sod-3<sup>b</sup> | $\downarrow 22.1 \pm 2.0$ |
|      |                   |                   |                    | Sod-4(gk101)<sup>b</sup>     | $\downarrow 21.9 \pm 0.2$ |
|      |                   |                   |                    | Daf-2; sod-4<sup>b</sup>     | $\uparrow 23.2$   |
|      |                   |                   |                    | Sod-2; daf-7(e1372)         | $\downarrow 24.3$ |
|      |                   |                   |                    | Daf-7(e1372) Mev-1(kn-1)    | $\downarrow 17.9$ |
| 50   | *(Galbadage and Hartman, 2008)* | 50 | 12°C | N2a              | $33.7 \pm 6.4$ |
|      |                   |                   | *NGM               | Daf-16(m27)<sup>b</sup>      | $\downarrow 29.9 \pm 8.0$ |
|      |                   |                   | E. coli OP50        | Clk-1(e2519)<sup>b</sup>     | $\uparrow 40.7 \pm 8.4$ |
|      |                   |                   |                    | Eat-2(ad465)<sup>b</sup>     | $\uparrow 36.6 \pm 12.6$ |
|      |                   |                   |                    | Daf-2(e1370)<sup>b</sup>     | $\uparrow 38.9 \pm 12.3$ |
|      |                   |                   |                    | 18.5°C                      | $19.2 \pm 4.7$   |
|      |                   |                   | *NGM               | N2a                          | $\downarrow 18.6 \pm 5.3$ |
|      |                   |                   | E. coli OP50        | Daf-16(m27)<sup>b</sup>      | $\downarrow 18.6 \pm 5.3$ |
|      |                   |                   |                    | Clk-1(e2519)<sup>b</sup>     | No numerical data |
|      |                   |                   |                    | Eat-2(ad465)<sup>b</sup>     | No numerical data |
|      |                   |                   |                    | Daf-2(e1370)<sup>b</sup>     | No numerical data |
|      |                   |                   |                    | 25°C                         | $12.6 \pm 3.0$   |
|      |                   |                   | *NGM               | N2a                          | $\downarrow 9.5 \pm 1.3$ |
|      |                   |                   | E. coli OP50        | Daf-16(m27)<sup>b</sup>      | $\downarrow 9.5 \pm 1.3$ |
|      |                   |                   |                    | Clk-1(e2519)<sup>b</sup>     | $\uparrow 18.7 \pm 4.3$ |
|      |                   |                   |                    | Eat-2(ad465)<sup>b</sup>     | $\uparrow 17.3 \pm 4.7$ |
|      |                   |                   |                    | Daf-2(e1370)<sup>b</sup>     | $\uparrow 38.7 \pm 15.2$ |
| 51   | *(Ghazi et al., 2009)* | 90 | 20°C | N2a              | $20.7 \pm 0.7$ |
|      |                   |                   | *NGM               | Daf-2(mu150)<sup>b</sup>     | $\uparrow 33.4 \pm 0.7$ |
|      |                   |                   | E. coli OP50        | Daf-2(e1368)<sup>b</sup>     | $\uparrow 32.7 \pm 0.7$ |
|      |                   |                   |                    | Daf-2(e1370)<sup>b</sup>     | $\uparrow 40.8 \pm 1.0$ |
|      |                   |                   |                    | Glp-1(e2141ts)<sup>b</sup>  | $\uparrow 23.2 \pm 0.4$ |
|      |                   |                   |                    | Eat-2(ad1116)<sup>b</sup>   | $\uparrow 27.3 \pm 0.6$ |
Table 4: Effect of differential genes expression on the mean and maximum lifespan of *C. elegans*.

| No. | Author       | No. of worms used | Culture conditions | Gene tested | Lifespan (days) |
|-----|--------------|-------------------|--------------------|-------------|-----------------|
|     |              |                   |                    |             | Mean            | Maximum |
| 1   | (Araiz et al., 2008) | No data           | 20°C *NGM* E. coli OP50 | N2a         | 18.9±0.1        | 28.0    |
|     |              |                   |                    | Ftt-1b      | ↓16.4±0.1       | ↑29.0   |
|     |              |                   |                    | Ftt-2b      | ↓15.6±0.1       | ↑31.0   |
|     |              |                   |                    | Daf-16(mgDf50)b | ↓13.9±0.1     | ↑24.0   |
|     |              |                   |                    | Daf-16;fft-1b | ↓14.0±0.3      | ↑29.0   |
|     |              |                   |                    | Daf-16;fft-2b | ↓12.8±0.1      | ↑20.0   |
|     |              |                   |                    | Daf-2(e1365)b | ↑31.3±0.7      | ↑42.0   |
|     |              |                   |                    | Daf-2;fft-1b | ↑25.4±0.3      | ↑38.0   |
|     |              |                   |                    | Daf-2;fft-2b | ↑23.4±0.4      | ↑38.0   |
|     |              | 124               | 20°C *NGM* E. coli OP50 | N2a         | 20.0            | 35.0    |
|     |              |                   |                    | Ftt-1b      | ↑25.0           | ↑43.0   |
|     |              |                   |                    | Daf-2(e1370)b | ↑26.0          | ↑41.0   |
|     |              | 121               |                    | Age-1(hx546)b | No data        | ↑41.0   |
|     |              |                   |                    | Fgt-1;daf-2b | ↑29.0           | ↑47.0   |
|     |              |                   |                    | Fgt-1;age-1b | ↑27.0           | ↑44.0   |
| 2   | (Feng et al., 2013) | 124               | 20°C *NGM* E. coli OP50 | N2a         | 16.3            | 27.0    |
|     |              |                   |                    | Age-1(hx546)b | ↑20.8          | ↑33.0   |
|     |              |                   |                    | Age-1;rme-1b | ↓13.1           | ↓25.0   |
|     |              |                   |                    | Age-1;rme-6b | ↑19.8           | ↑28.0   |
|     |              |                   |                    | Age-1;rme-8b | ↑19.1           | ↑32.0   |
|     |              |                   |                    | Clk-1(e2519)b | ↑17.9          | ↑29.0   |
|     |              |                   |                    | Clk-1;rme-1b | ↑18.3           | ↑30.0   |
|     |              |                   |                    | Eat-2(ad465)b | ↑18.2           | ↑30.0   |
|     |              |                   |                    | Eat-2;rme-1b | ↑18.4           | ↑24.0   |
|     |              |                   |                    | Eat-2;rme6b  | ↑18.4           | ↑24.0   |
|     |              |                   |                    | Eat-2;rme-8b | ↑19.8           | ↑30.0   |
|     |              |                   |                    | Rme-1b      | ↑17.6           | ↑28.0   |

*NGM = Nematode Growth Medium*
### Table 5: Effect of differential genes expression on the maximum lifespan of *C. elegans.*

| No. | Author          | No. of worms used | Culture conditions | Gene tested                          | Lifespan (days) |
|-----|-----------------|-------------------|--------------------|---------------------------------------|-----------------|
| 1   | (Lee et al., 2009) | 36                | 20°C               | N2a                                   | 32.0            |
|     |                 |                   | *NGM E. coli OP50  | Daf-16b                               | ↓22.0           |
|     |                 |                   |                    | Hsf-1b                                | ↓15.0           |
|     |                 |                   |                    | Daf-2(e1370)b                         | ↑80.0           |
|     |                 |                   |                    | Daf-2(e1368)b                         | ↑45.0           |
|     |                 |                   |                    | Aqp-1b                                | ↓30.0           |
| 2   | (Honda et al., 2010) | No data          | 20°C               | N2a                                   | 30.0            |
|     |                 |                   | *NGM E. coli OP50  | Daf-2b                                | ↑75.0           |
|     |                 |                   |                    | Sod-2; daf-2b                         | ↑65.0           |
|     |                 |                   |                    | Sod-2; daf-2; Ex[sod-2]c              | ↑100.0          |
|     |                 |                   |                    | Daf-2; sod-3b                         | ↑100.0          |
|     |                 |                   |                    | Daf-2; sod-3; Ex[sod-3]c              | ↑75.0           |
| 3   | (Khare et al., 2011) | No data          | 25°C               | N2a                                   | 17.0            |
|     |                 |                   | *NGM E. coli OP50  | Transgenic strains:                   | ↑25% (25.0)     |
|     |                 |                   |                    | PL51c                                 |                |
| 4   | (Lehrbach et al., 2012) | 40               | 25°C               | N2a                                   | 15.0            |
|     |                 |                   | *NGM E. coli       | Pash-1tsb                             | ↓10.0           |
|     |                 |                   | HT115              |                                       |                |
| 5   | (Seo et al., 2013) | 30                | 20°C               | N2a                                   | 30.0            |
|     |                 |                   | *NGM E. coli OP50  | Hsf-1(sy441)b                         | ↓25.0           |
|     |                 |                   |                    | Rsks-1(tm1714)b                       | ↑40.0           |
|     |                 |                   |                    | Daf-16(mu86)b                         | ↓20.0           |
|     |                 |                   |                    | Daf-2(e1370)b                         | ↑58.0           |
| 6   | (Johnson et al., 2014) | 25               | 20°C Liquid        | N2a                                   | 25.1±0.9        |
|     |                 |                   | E. coli HT115      | Daf-2(e1370)b                         | ↑60.5±2.4       |
|     |                 |                   |                    | Daf-2; mxx-1(tm1530)b                 | ↑83.9±3.3       |
|     |                 |                   |                    | Daf-2; mxx-2(tm1516)b                 | ↑43.2±3.3       |
|     |                 |                   |                    | Daf-3(tm4940)b                        | ↓22.0±1.9       |
|     |                 |                   |                    | Eat-2(ad465)b                         | ↑44.1±2.6       |
|     |                 |                   |                    | Eat-2; mxx-1b                         | ↑40.1±2.7       |
|     |                 |                   |                    | Eat-2; mxx-2b                         | ↓23.1±1.1       |
|     |                 |                   |                    | Mdl-1(tm311)b                         | ↑40.3±3.2       |
|     |                 |                   |                    | Mml-1(ok849)b                         | ↓22.4±1.5       |
|     |                 |                   |                    | Mxl-1(tm1530)b                        | ↑35.7±1.5       |
|     |                 |                   |                    | Mxl-2(tm1516)b                        | ↑21.2±1.3       |
|     |                 |                   |                    | Mxl-3(ok1947)b                        | ↑41.6±3.7       |
|     |                 |                   |                    | Daf-16(mgDf47)b                       | ↓22.8±2.4       |
| 7   | (Singh et al., 2016) | No data          | 20°C               | N2a                                   | 32.0            |
|     |                 |                   | *NGM E. coli OP50  | Daf-16<sup>a</sup>                     | ↓20.0           |
|     |                 |                   |                    | Pha-4<sup>b</sup>                     | ↓28.0           |
|     |                 |                   |                    | Zfp-1(ok554)<sup>b</sup>              | ↓30.0           |
|     |                 |                   |                    | Gfl-1<sup>b</sup>                     | ↓28.0           |

<sup>a</sup>NGM = Nematode Growth Medium
Table 6: (Continue from Table 5) Effect of differential genes expression on the maximum lifespan of *C. elegans*.

| No. | Author                      | No. of worms | Culture conditions | Gene tested                   | Lifespan (days) |
|-----|-----------------------------|--------------|--------------------|--------------------------------|-----------------|
| 8   | (Loucks *et al.*, 2016)    | 100          | 20°C *NGM* E. coli OP50 | N2a, Perg-1(tm2597)b, Daf-16b, Perg-1;daf-16b, Daf-2b, Perg-1;daf-2b, Eat-2b, Pcrg-1;eat-2b | 30.0 ↑28.0 ↓20.0 ↑55.0 ↑60.0 ↑50.0 |
| 9   | (Li *et al.*, 2016)        | 100          | 20°C *NGM* E. coli OP50 | N2a, Scav-3(qx193)b, Daf-2(e1370)b, Daf-2;scav-3b, Daf-16(mu86)b, Daf-16;daf-2b, Daf-16;daf-2;scav-3b, Scav-3(ok1286)b, Scav-3(tm3659)b | 30.0 ↑22.0 ↑73.0 ↑63.0 ↓25.0 ↓20.0 ↓25.0 |
| 10  | (Xu *et al.*, 2016)        | 50-100       | 20°C *NGM* E. coli OP50 | N2a, Daf-2(e1370)b, Daf-16(mu86)b, Age-1(hx546)b, Daf-16bkob | 30.0 ↑28.0 ↓26.0 ↑34.0 ↓23.0 |
| 11  | (Prasanth *et al.*, 2016)  | 20           | 20°C *NGM* & liquid E. coli OP50 | N2a, Daf-2(e1370)b | 15 days on solid media 15 days on liquid media ↑42 days on liquid media ↑40 days on solid media |
| 12  | (Maklakov *et al.*, 2017)  | 50           | 20°C *NGM-*nystatin E. coli OP50 | N2a, Age-1(hx546)b | 24.0 ↑40.0 |

*NGM= Nematode Growth Medium*
Table 7: Effect of differential genes expression on the mean and median lifespan of *C. elegans*.

| No. | Author | No. of worms used | Culture conditions | Gene tested | Lifespan (days) | Mean | Median |
|-----|--------|-------------------|--------------------|-------------|-----------------|------|--------|
| 1   | (Tvermoes et al., 2010) | 50-65 | 20°C *E. coli* OP50 | Numr-1(ok2239)b | ↓ (No numerical data) | (No numerical data) |
|     |        |                  |                    | Numr-1(tm2775)b | ↓ (No numerical data) | (No numerical data) |
|     |        |                  |                    | Transgenic strains: | ↑ (No numerical data) | (No numerical data) |
|     |        |                  |                    | JF88(mtEx63)c |         | 9    |
|     |        |                  |                    | T[356(zis356)]{daf-16;rol-6}c | ↑ (No numerical data) | (No numerical data) |
|     |        |                  |                    |                  |           |      |
| 2   | (Wang et al., 2010) | 100 | 20°C *E. coli* OP50 | N2a | 22.64±0.2 | 23.0 |
|     |        |                  |                    | Skn-1(zu135)b | ↓20.29±0.2 | ↓20.0 |
|     |        |                  |                    | Ile-2(eIF4F)b | ↑24.86±0.4 | ↑25.0 |
|     |        |                  |                    | Skn-1;iie-2b | ↓21.11±0.4 | ↓19.0 |
|     |        |                  |                    | Ifg-1(eIF4F)b | ↑27.91±0.5 | ↑28.0 |
|     |        |                  |                    | Skn-1;ifg-1b | ↑26.21±0.5 | ↑25.0 |
|     |        |                  |                    | Eif-1(PI)C | ↑28.16±0.2 | ↑29.0 |
|     |        |                  |                    | Skn-1;iie-1b | ↓22.18±0.3 | 23.0 |
|     |        |                  |                    | eIF-1A(PIC) | ↑26.84±0.5 | ↑27.0 |
|     |        |                  |                    | Skn-1;iel-1Ab | ↓21.62±0.4 | ↓22.0 |
|     |        |                  |                    | Skn-1(zu67)b | ↓18.33±0.4 | ↓17.0 |
|     |        |                  |                    | Skn-1;iie-2b | ↓18.31±0.4 | ↓17.0 |
|     |        |                  |                    | Skn-1;ifg-1b | ↑25.88±0.6 | ↑26.0 |
|     |        |                  |                    | Skn-1;iie-1b | ↑20.42±0.4 | ↑19.0 |
|     |        |                  |                    | Daf-16(mdF47)b | ↓19.74±0.4 | ↓20.0 |
|     |        |                  |                    | Daf-16;iie-2b | ↓19.77±0.4 | ↓20.0 |
|     |        |                  |                    | Daf-16;skn-1b | ↓16.91±0.3 | ↓17.0 |
|     |        |                  |                    | Daf-16;ifg-1b | ↑23.61±0.4 | ↑25.0 |
|     |        |                  |                    | Daf-16;skn-1 ifg-1b | ↓18.72±0.4 | ↓18.0 |
|     |        |                  |                    | Daf-16;eif-1b | ↓20.91±0.3 | ↓21.0 |
|     |        |                  |                    | Daf-16;skn-1;eif-1b | ↓16.42±0.2 | ↓16.0 |
| 3   | (Masse et al., 2008) | 30 | 20°C *E. coli* OP50 | N2a | 16.2±0.4 | 15.0 |
|     |        |                  |                    | Smg-1(tm869)b | ↑19.8±0.3 | ↑21.0 |
|     |        |                  |                    | Rrf-3(pk1426)b | ↑16.9±0.2 | 15.0 |
|     |        |                  |                    | Daf-18(e1375);rfl-3b | ↓12.7±0.2 | ↓12.0 |
|     |        |                  |                    | Tax-4(p678);rfl-3b | ↑22.6±0.5 | ↑24.0 |
| 4   | (Saul et al., 2009) | 499 | 20°C *E. coli* OP50 | N2a | 16.91 | 16.13 |
|     |        |                  |                    | Age-1(hx546)b | ↓15.90 | ↓13.21 |
|     |        |                  |                    | Akt-2(ok393)b | ↑19.62 | ↑18.66 |
|     |        |                  |                    | Daf-2(m577)b | ↑18.53 | ↑16.03 |
|     |        |                  |                    | Daf-12(m20) | ↓10.53 | ↓9.42 |
|     |        |                  |                    | Daf-16(mdF50)b | ↓11.79 | ↓11.35 |
|     |        |                  |                    | Skn-1(zu67)b | ↓9.19 | ↓8.46 |
| 5   | (Xu and Kim, 2012) | 246 | 20°C *E. coli* OP50 | N2a | 14.3 | 13 |
|     |        |                  |                    | Daf-2(e1370)b | ↑48.9 | ↑49.0 |
|     |        |                  |                    | Egl-27(we3)b | ↑27.8 | ↑28.0 |
|     |        |                  |                    | Daf-2;daf-16(mu86)b | ↑24.0 | ↑25.0 |
|     |        |                  |                    | Daf-2;egl-27(we3)b | ↑21.5 | ↑20.0 |

*NGM = Nematode Growth Medium*
Table 8: Effect of differential genes expression on the median lifespan of *C. elegans*.

| No. | Author                          | No. of worms used | Culture conditions | Gene tested | Median |
|-----|---------------------------------|-------------------|--------------------|-------------|--------|
| 1   | (Martorell et al., 2011)        | 300               | 20°C               | N2a         | 15.0   |
|     |                                 |                   |                     | Sir-2.1(ok434)b | No effect |
|     |                                 |                   |                     | Daf-16(mgDf50)b | No effect |
|     |                                 |                   |                     | Daf-2(e1370)b | ↑20.0   |
| 2   | (Rahman et al., 2010)           | 85-125            | 20°C               | N2a         | 15.9±3.6 |
|     |                                 |                   |                     | Oga-1(ok1207)b | ↑20.9±4.1 |
|     |                                 |                   |                     | Ogt-1(ok1474)b | ↓12.9±1.9 |
|     |                                 |                   |                     | Daf-2(e1370)b | ↑28.6±3.5 |
|     |                                 |                   |                     | Daf-16(mu86)b | ↓14.3±2.5 |
|     |                                 |                   |                     | Age-1(hx546)b | ↑25.6±4.1 |
|     |                                 |                   |                     | Sgk-1(ok538)b | ↑29.8±3.2 |
|     |                                 |                   |                     | Pdk-1(mg142)b | ↓14.8±1.7 |
|     |                                 |                   |                     | Akt-1(mg144)b | ↓11.5±2.1 |
| 3   | (Evans et al., 2008)            | 300               | 20°C               | N2a         | 36.0   |
|     |                                 |                   |                     | Akt-1(ok525)b | No effect |
|     |                                 |                   |                     | Akt-2(ok393)b | ↑40.0   |
|     |                                 |                   |                     | Sgk-1(ok538)b | ↓35.0   |
| 4   | (Stout et al., 2013)            | 30                | 25°C               | N2a         | 20.0   |
|     |                                 |                   |                     | Daf-16(mu86)b | ↓15.0   |
|     |                                 |                   |                     | Aars-2b     | ↑22.0   |
| 5   | (Piazzesi et al., 2016)         | No data           | 20°C               | N2a         | 24±1.1 |
|     |                                 |                   |                     | His-72(tm2066);his-71(ok2289)b | No effect (24±1.5) |
|     |                                 |                   |                     | His-72p::his-72::GFPb | ↑25.4±1.4 |
|     |                                 |                   |                     | Daf-2(e1370)b | ↑44±4.4 |
|     |                                 |                   |                     | Daf-2;his-72b | ↑40±1.4 |
|     |                                 |                   |                     | Daf-2;his-71b | ↑32±5.9 |
|     |                                 |                   |                     | Daf-16(mu86):daf-2b | ↓15±0.3 |
|     |                                 |                   |                     | Daf-16;daf-2;his-72;his-71b | ↓15±0.7 |
|     |                                 |                   |                     | No effect (24±0.7) | ↑30±4.0 |
|     |                                 |                   |                     | His-72p::hh3.3::ha;his-71p::hh3.3::mycb | ↓19±1.5 |
|     |                                 |                   |                     | Nuo-6(qm200)b | Nuo-6(qm200);his-72;his-71b | 25°C |
|     |                                 |                   |                     | N2a         | 16±0.7 |
|     |                                 |                   |                     | Glp-1(bn18)b | ↑26±0.5 |
|     |                                 |                   |                     | Glp-1;his-72(tm2066);his-71(ok2289)b | ↑19±1.3 |
|     |                                 |                   |                     | Glp-1;his-72p::hH3.3::HA;his-71p::hH3.3::Mycb | ↑23±1.2 |
|     |                                 |                   |                     | Glp-1;his-72p::hH3.3::HA;his-71p::hH3.3::Mycb | ↑22±1.2 |
|     |                                 |                   |                     | Glp-1;his-72p::hH3.3::HA;his-71p::hH3.3::Mycb | ↑25.0 |
|     |                                 |                   |                     | Glp-1;his-72p::hH3.3::HA;his-71p::hH3.3::Mycb | ↑25±0.3 |

*NGM = Nematode Growth Medium
involved in the IIS pathway. Most of the studies found that knockdown of daf-2 and age-1 genes extended lifespan while knockdown of genes such as daf-16, skn-1, hsf-1, and sir-2.1 resulted in a shortened lifespan.

*C. elegans* is known to live between 25-30 days in normal conditions. A total of 51 studies have demonstrated that the lifespan of *C. elegans* was extended by 2-fold following depletion of daf-2 expression. The increased lifespan could be due to the fact that inhibition of DAF-2 causes decreased of its binding to the insulin receptor substrate (IRS)/IST-1 leading to dephosphorylation and deactivation of phosphoinositase-3 kinase (AGE-1) that encodes phosphatidylinositol-3-OH kinase (P13K) which responsible to convert phosphatidylinositol-3 (PIP₃) to phosphatidylinositol-2 (PIP₂) (Kenyon, 2010). Decreased PIP₃ level will dephosphorylate phosphoinositol-dependent kinase 1 (PDK-1), serine/threonine-specific protein kinase B (AKT-1/2) (Paradis and Ruvkun, 1998), and glucocorticoid-inducible kinase-1 (SGK-1) which will then activate DAF-16 (downstream transcription factor FOXO). Hence, enhanced cytoplasm-to-nucleus translocation will activate expressions of genes that lead to longevity (Altintas et al., 2016) such as heat shock proteins (HSPs) and antioxidants (Hu, 2007). Studies in this review showed an extended lifespan of daf-2 knockdown to be around 30 to 45 days. Most of the studies used daf-2(e1370) strain as daf-2 knockdown mutant because other daf-2 mutant strains such as daf-2(m41) is a class 1 allele of daf-2 mutant while daf-2(e1370) is a class 2 allele. Daf-2(m41) mutations trigger dauer formation at 25°C. Other than that, it is temperature-sensitive and less pleiotropic than alleles such as daf-2(e1370) (Gems et al., 1998). Therefore, daf-2(e1370) is considered to be the most ideal strain for studying daf-2 in influencing *C. elegans*’s lifespan. Lifespan extension of knockdown daf-2 mutants depends on transcription factors DAF-16 and DAF-12 (Ogg et al., 1997; Hsin and Kenyon, 1999; Matyash et al., 2004). Different daf-2 class mutants and corresponding phenotypic traits are believed to result in a common and different downstream unknown complex processes that influence regulation of daf-16 gene product (Gems et al., 1998; Nanji et al., 2005).

Furthermore, the results from 40 studies showed a decrement of *C. elegans*’s lifespan following daf-16 knockdown. The *C. elegans* IIS pathway connects nutrient levels to metabolism, growth, development, longevity, and behaviour (Holzenberger et al., 2003). This pathway is regulated by the binding of insulin-like peptide ligands (ILPs) to the insulin/IGF-1 trans-membrane receptor (IGFR) ortholog DAF-2, which then influences the activation of DAF-16 and transcriptional activity of a gene that prolong lifespan. Therefore, knockdown of daf-16 results in a shortened lifespan. Studies reported in this review found a reduction in the lifespan of daf-16 knockdown mutant when compared to wild-type. Based on the studies reviewed, daf-16 mutant *C. elegans* live approximately 8 to 20 days. A total of 21 studies used daf-16(mgDf50) strain as daf-16 mutant. Daf-16(mgDf50) strain is a mutant with complete elimination of the daf-16 coding region. This is considered to be the most ideal strain to be used to study the effect of daf-16 on the lifespan of *C. elegans*. Another optimal daf-16 mutant strain used is daf-16(mib86) mutant, which is a dauer defective worm. Dauer is a stage where the nematodes are on its defensive mode when unfavourable conditions are encountered. At the dauer stage, the nematode produces a cuticle that coats their body for protection and halts eating hence to suspend growth (Bargmann and Horvitz, 1991). This strain is commonly used to study the effect of environmental stressors on the worms’ lifespan because the dauer stage helps the nematodes to survive in unfavourable conditions (Erkut et al., 2013).

The knockdown of age-1 expression increases *C. elegans* lifespan, as reported by 13 studies. The inhibition of AGE-1 contributes to the extension of lifespan as it plays a vital role in the production of PIP₃. The decreased activity of AGE-1 will increase the activity of PTEN phosphatase (DAF-18) and decrease the activity of phosphoinositide-3 kinase, which converts PIP₃ to PIP₂ Kenyon (2010). Decreased PIP₃ levels lead to decreased activities of PDK-1 and AKT-1/2 as well as activation of DAF-16, which promotes longevity (Paradis and Ruvkun, 1998). Studies included in this review reported lifespan extension of age-1 knockdown mutants to be around 17 to 47 days. The age-1(hx546) strain was used in these studies mainly because age-1 mutants have a long life with normal fertility and good tolerance to stress and temperature changes (Friedman and Johnson, 1988).

SKN-1 function as cofactors of DAF-16. Similar to in daf-16, skn-1 is also needed for the extension of lifespan (Ewald et al., 2015). This is because SKN-1 plays a major role in various crucial processes needed for lifespan extension, such as protein synthesis in the endoplasmic reticulum (ER), metabolism, and maintaining protein homeostasis when under normal conditions and also when in response to stresses (Blackwell et al., 2015) SKN-1 also contributes to protection against pathogenic infection, which improves the survival of *C. ele-
The study was done by (Rathor et al., 2015), showed an increased in C. elegans’s lifespan following the skn-1 knockdown. However, seven other studies reported the opposite where knockdown of skn-1 is found to decrease the lifespan of C. elegans. SKN-1 is critical for oxidative stress resistance and promotes longevity under reduced IIS signaling, dietary restriction (DR), and normal conditions (Tullet et al., 2008).

One of the most important downstream transcription factors of IIS is heat shock transcription factor 1 (HSF-1). HSF plays essential and evolutionary conserved roles in the activation of heat shock-inducible gene expression. HSFs are recognized as regulators of stress-induced gene expression, besides contributing to more complex organismal physiological processes such as development, growth, aging, immunity, and reproduction. HSF-1 is also known to regulate protein folding and gene expression in response to heat stress. It modulates longevity by upregulating the chaperone network and enhancing the proper folding of proteins (Hsu et al., 2003; Morley and Morimoto, 2004; Douglas et al., 2015). Some studies reported that knockdown of hsf-1 gene decreases the lifespan of C. elegans by about 8% from wild-type. Heat shock protein-90 (HSP-90) is another chaperone protein which helps to repair misfolded proteins that accumulate during stress. This protein also has essential functions in protein synthesis, processing, and degradation, which are activated by an exertion of HSF-1 cytoplasm-to-nucleus translocation (Parsell and Lindquist, 1993; Young et al., 2004). HSF-1 acts in parallel with DAF-16 to provide pathogen resistance hence extending lifespan. A study done on HSF-1 showed that overexpression of hsf-1 significantly enhanced C. elegans resistance to P. aeruginosa infection. This indi-
licated that the chaperone system recognized and degraded bacterial virulence factors or functions by proper folding of effector molecules in the immune system (Singh and Aballay, 2006). Studies have shown that knockdown of hsf-1 drastically reduces the lifespan of *C. elegans*. Transcription factor HSF-1 guides DAF-16/FOXO activity and cooperatively induce transcription of a subset of target genes, including HSPs involved in proteostasis. Daf-16, hsf-1, and skn-1 mutants have been to be more sensitive to oxidative and thermal stress as compared to the wild-type nematodes (Hsu et al., 2003; Uno and Nishida, 2016).

SIR-2.1 is a sirtuin, member of the nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase. It is directly linked to cellular nutrient signaling through NAD⁺ (Guarente, 2008; Houtkooper et al., 2010). SIR-2.1 is responsive to metabolic changes in the cellular environment, including nutrient/energy availability and cellular stress (Lin et al., 2003). SIR-2.1 increases the lifespan of *C. elegans* through DAF-16 (Tissenbaum and Guarente, 2001). SIR-2.1 binds to DAF-16 in response to cellular stress and promotes DAF-16 activation that results in longevity. A total of ten studies determined the effect of *sir-2.1* gene on the lifespan of *C. elegans*. Most of these studies showed consistent effects of SIR-2.1 on the lifespan. A total of five studies found a reduction in lifespan when *sir-2.1* was knocked down, while four studies showed an increased in lifespan when *sir-2.1* was overexpressed. In contrast, a study done by (Martorell et al., 2011) found that *sir-2.1* had no effect on the lifespan of *C. elegans*. SIR2 is a positive regulator of lifespan in *Saccharomyces cerevisiae* and in *C. elegans* (Kaebelerlein et al., 1999). Overexpression of *sir-2.1*, the *C. elegans* homolog of SIR2, has been reported to extend lifespan in a DAF-16-dependent manner. SIR-2.1 binds to DAF-16 in response to cellular stress and promote DAF-16 activation, which leads to longevity. All of the studies in this review used *sir-2.1(ok434)* strain as *sir-2.1* mutant except for study done by (Wang et al., 2010), which used *sir-2.1(zu67)* strain. Studies in this review showed lifespan extension of *sir-2.1* overexpression to be around 13 to 28 days while *sir-2.1* knockout decreased lifespan to around 12 to 17 days.

Variations in the number of days of survival seen in the studies reported here were mostly due to the difference in the experimental conditions used. *C. elegans* survived well between 15°C - 25°C. The worms will enter a stage of dauer at temperatures beyond this range. Experiments carried out at 25°C observed a shorter lifespan of the nematode as compared to 20°C. Elsewhere studies performed at 15°C found the longer average lifespan of *C. elegans*. *Escherichia coli* strain OP50 (*E. coli* OP50) and Nematode Growth Medium (NGM) are standard laboratory *C. elegans* food and media as it has been used in *C. elegans* research for decades. Different strains of *E. coli* did not show any prominent effects on lifespan. However, a higher mean lifespan was observed in worms fed with live OP50 under low-density feeding (LDF) conditions (OD=0.18), whereas lower mean lifespan was seen under high-density feeding (HDF) conditions (OD=1.5). This shows that an increasing amount of food correlates with decreased lifespan in adult *C. elegans* as the worms obtain most of their energy from this microbe. *C. elegans* also have a longer lifespan in liquid media as compared to solid media. This is probably due to the lower restriction available in liquid media than in solid media. Besides, additional components such as streptomycin, ampicillin, and nystatin in NGM may help to prevent contamination of the media.

A few studies have reported on the effect of *ins-18*, *numr-1/-2*, *sgk-1*, and *rngs-1* genes on the lifespan of *C. elegans*, although these genes play vital roles in resistance. Results found by Matsunaga et al. (2012) indicated that at the adult stage, *ins-18* is needed for lifespan enhancement. According to his study, deletion of *ins-18* due to the relative dominance of agonist binding to DAF-2 reduced larval diapause. The overexpression of *ins-18* induced larval diapause, which is important for defence against pathogens. High levels of INS-18 will bind to DAF-2 and inhibit agonist binding, thus preventing the binding of other DAF-2 agonists. Based on the results, it was concluded that *ins-18* is required for longevity. The expression of *numr-1/-2* is associated with resistance to metal toxicity. Knockdown of *numr-1/-2* expression increased sensitivity to cadmium exposure while overexpression of *numr-1/-2* increases lifespan in the presence and absence of metal. However, under control conditions, lower expression of *numr-1/-2* does not significantly reduce wild-type lifespan, but in the presence of metals, lower lifespan is observed. This suggests that *numr-1/-2* contribution for longer lifespan needs to be accompanied with other genes. According to the result shown in the sequence analysis of *numr-1* and *numr-2*, the regulatory regions of *numr-1/-2* contain consensus binding sites for both SKN-1 and DAF-16. *Numr-1* and *numr-2* may perform the biological activities necessary to increase resistance and longevity that are mediated by the IIS pathway (Cui et al., 2007). Two of the studies from this review were done on *sgk-1*, which acts downstream of *daf-2* in the IIS pathway shows an increased in lifespan (Rahman et al., 2010; Akhoon...
et al., 2016). Serum-and glucocorticoid-regulated kinase gene (sgk-1) act similar to Akt-1 in lifespan control by phosphorylating and inhibiting the nuclear translocation of DAF-16/FOXO (Chen et al., 2013). The regulator of G protein signaling-1 (rgs-1) plays an important role in paraquat-induced oxidative stress (Wu et al., 2017). As compared to wild-type, rgs-1(nr2017) mutant displayed significant resistance to paraquat (PQ) toxicity, where a 20% increase in mean survival time was observed. Rgs-1 mutant results in a decrease in overall ROS levels compared to wild-type after PQ exposure. This suggests that RGS-1 modulates PQ resistance in a DAF-16-dependent manner. Both of the daf-16(mu86);rgs-1(nr2017) double mutant and daf-16(mu86) single mutant were sensitive to PQ. The effect of RGS-1 was completely suppressed by the daf-16 mutant, indicating that rgs-1 depends on daf-16 to modulate PQ resistance. Loss of rgs-1 promotes lifespan relying on age-1 and daf-16 as rgs-1 showed significant extension in mean lifespan. A shorter lifespan was seen in daf-16(mu86) than wild-type but had a similar lifespan to the daf-16(mu86);rgs-1(nr2017) suggesting that the long-lived phenotype associated with rgs-1 requires daf-16 (Lin et al., 2011).

Genes in the insulin/insulin-like signaling (IIS) pathway influences the lifespan of C. elegans by regulating vital pathways for the survival of the worm. Knockdown of genes, namely, daf-2 and age-1 and overexpression of hsf-1, daf-16, skn-1, and sir-2.1, have been unanimously reported to promote longevity. The roles of these genes have well been established previously. However, whether the modulation of expression of these genes also leads to improved healthspan of the worms is still unclear. The results of these studies renders future researchers to study the effect of the homologous genes in higher-order organismal such as mice, to establish the possibility of lifespan extension through modulation of genes expression and to elucidate the healthspan of organisms with a prolonged lifespan.

CONCLUSIONS

The documented evidence in this review suggests that IIS pathway genes influence the lifespan of C. elegans through various mechanisms. Since their roles are well conserved in C. elegans. These genes may be targets for future interventional studies aimed to enhance longevity.

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