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RESEARCH ARTICLE

A collective analysis of lifespan-extending compounds in diverse model organisms, and of species whose lifespan can be extended the most by the application of compounds

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Abstract Research on aging and lifespan-extending compounds has been carried out using diverse model organisms, including yeast, worms, flies and mice. Many studies reported the identification of novel lifespan-extending compounds in different species, some of which may have the potential to translate to the clinic. However, studies collectively and comparatively analyzing all the data available in these studies are highly limited. Here, by using data from the DrugAge database, we first identified top compounds in terms of their effects on percent change in average lifespan of diverse organisms, collectively (n = 1728). We found that, when data from all organisms studied were combined for each compound, aspirin resulted in the highest percent increase in average lifespan (52.01%), followed by minocycline (27.30%), *N*-acetyl cysteine (17.93%), nordihydroguaiaretic acid (17.65%) and rapamycin (15.66%), in average. We showed that minocycline led to the highest percent increase in average lifespan among other compounds, in both *Drosophila melanogaster* (28.09%) and *Caenorhabditis elegans* (26.67%), followed by curcumin (11.29%) and gluconic acid (5.51%) for *D. melanogaster* and by metformin (26.56%), resveratrol (15.82%) and quercetin (9.58%) for *C. elegans*. Moreover, we found that top 5 species whose lifespan can be extended the most by compounds with lifespan-extending properties are *Philodina acuticornis*, *Acheta domesticus*, *Aeolosoma viride*, *Mytilina brevispina* and *Saccharomyces cerevisiae* (211.80%, 76%, 70.26%, 55.18% and 45.71% in average, respectively). This study provides novel insights on lifespan extension in model organisms, and highlights the importance of databases with high quality content curated by researchers from multiple resources, in aging research.

Keywords Aging · *Caenorhabditis elegans* · *Drosophila melanogaster* · Lifespan · Minocycline · Model organisms · Philodina acuticornis

Introduction

Aging is a major risk factor for many diseases in humans; thus, the identification of compounds that extend lifespan/healthspan or delay aging is of high importance in aging research (Moskalev et al. 2016). Numerous studies reported the data on lifespan-extending compounds on model organisms including

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worms, flies, yeast and mice (Taormina et al. 2019; Holtze et al. 2021). Some of these compounds may have the potential to translate to the clinic, whereas some may not, due to the presence of species-specific mechanisms. However, species-specific effects of each of these compounds on lifespan change are highly understudied. Similarly, comparative analysis of different compounds in terms of lifespan change in particular model organisms (for example, minocycline vs quercetin in *Caenorhabditis elegans*) or in diverse species combined (for example, aspirin vs resveratrol in all model organisms studied collectively) is also lacking. Furthermore, which model organisms are relatively more prone to be manipulated by aging-related drugs in terms of lifespan extension compared to other species has not been studied in detail, previously, mostly due to the lack of sufficient data.

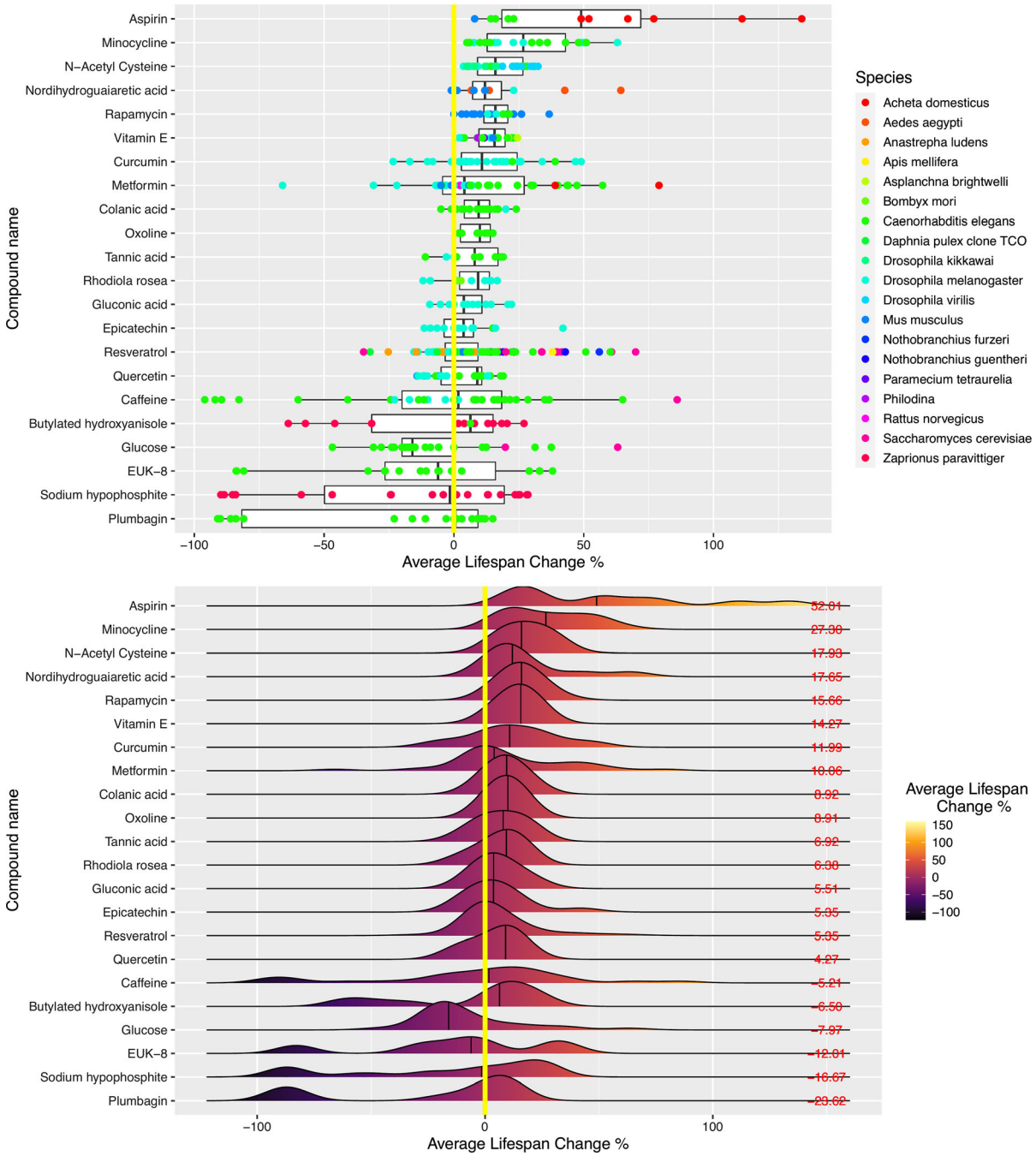
In the present study, using data from the DrugAge database, we first compared the mean percent lifespan change caused by different compounds by averaging data from multiple species for each compound (Barardo et al. 2017). We found that, when data from multiple organisms were combined for each drug (i.e. the effect of a compound not on a particular species but on all species studied for that compound), aspirin (acetylsalicylic acid) resulted in the highest average lifespan extension percentage, followed by minocycline, *N*-acetyl cysteine, nordihydroguaiaretic acid and rapamycin. Some drugs showed different modes of distribution (such as multimodal distribution) in terms of percent change in average lifespan, possibly pointing to their high species-specificity in the case of multimodal distribution. Moreover, we found that minocycline caused the highest percent change in average lifespan in both *Drosophila melanogaster* and *C. elegans*, followed by curcumin and gluconic acid in *D. melanogaster*, and by metformin and resveratrol in *C. elegans*. We showed that organisms whose lifespan can be manipulated the most by the use of compounds are *Philodina acuticornis* (a species of freshwater bdelloid rotifers), *Acheta domesticus* (house cricket), *Aeolosoma viride* (an asexually reproducing annelid/segmented worm), *Mytilina brevispina* (a rotifer) and *Saccharomyces cerevisiae* (yeast), based on currently available data. This study, by analyzing a dataset manually curated from 469 different studies (Barardo et al. 2017), reports different aspects of lifespan-extending compounds on diverse model organisms collectively, which are not possible with limited data reported in a single study.

Fig. 1 Top compounds in terms of their effects on average lifespan change in diverse organisms collectively. Percent change in average lifespan of organisms treated with longevity-extending compounds, when data from all organisms studied were combined for each compound. Top plot: Compounds were ordered as the compound which caused the highest percent increase in average lifespan in all organisms combined, given at the top of the plot. Data points for each species were given a different color. Yellow vertical line indicates no change (0%) in average lifespan. Vertical lines in boxplots indicates the median value. Legend shows the color code for each species. Bottom plot: Distribution of the percent change in average lifespan for each drug, when data from all organisms studied were combined per compound. Yellow vertical line indicates no change (0%) in average lifespan. Values in red at the end of *x* axis for every *y* value indicate mean percent change in average lifespan for each compound. Compounds were ordered as the compound which caused the highest percent increase in average lifespan (aspirin, 52.01%) in all organisms combined, given at the top of plot. Legend shows the color scale indicating percent change in average lifespan ▶

Materials and methods

Dataset

In this study, we used data from the DrugAge database of aging-related drugs (http://genomics.senescence.info/drugs/) [Build 3 (09/07/2019)] (Barardo et al. 2017). This dataset (n = 1823) contains data on the effect of different compounds on average or maximum lifespan change in diverse organisms. For some compounds, data for different drug concentrations/dosages are available; however, we combined data for all concentrations of each compound in the analysis, and analyzed altogether. Sample sizes (n) are 1782 and 556 for average lifespan change and maximum lifespan change, respectively; thus, based on its larger sample size, we focused on the effects of compounds on the average lifespan change percentage. Data for average lifespan change is available for 27 different species [*A. domesticus* (n = 8), *Aedes aegypti* (n = 5), *A. viride* (n = 5), *Anastrepha ludens* (n = 25), *Apis mellifera* (n = 1), *Asplanchna brightwelli* (n = 15), *Bombyx mori* (n = 2), *Brachionus manjavacas* (n = 6), *C. elegans* (n = 962), *Ceriodaphnia affinis* (n = 1), *Daphnia pulex clone TCO* (n = 4), *D. bipectinata* (n = 6), *D. kikkawai* (n = 8), *D. melanogaster* (n = 469), *D. virilis* (n = 12), *Mus musculus* (n = 104), *Musca domestica* (n = 4), *M. brevispina* (n = 4), *Nothobranchius furzeri* (n = 3), *N. guentheri* (n = 6), *Paramecium tetraurelia* (n = 5), *Philodina*



(n = 1), *P. acuticornis* (n = 3), *Podospora anserina* (n = 1), *Rattus norvegicus* (n = 29), *S. cerevisiae* (n = 51) and *Zaprionus paravittiger* (n = 42)].

When we group by compounds, we filtered out compounds with less than or equal to 10 data points; whereas when we group by species, we filtered out species with less than or equal to 2 data points. In all figures, the mean of percent change in average lifespan decreases from top to bottom of the plot, in terms of compounds (Figs. 1 and 2) or species (Fig. 3). Mean values of percent change in average lifespan for each

variable (compound or species) were given at the end of *x* axis (at the right) for each variable at the *y* axis.

We should also note that certain strains of *D. melanogaster* and *C. elegans* are represented more in the dataset, whereas some strains are highly under-represented. We indicated strain-wise distributions in Fig. 2 to highlight this issue.

Data analysis and visualization

Data analysis and visualization was performed in R programming environment [R version 4.0.2 (2020-06-22)] in the present study (R Core Team 2020; Grolemund and Wickham 2017). Following R packages were used throughout the study: tidyverse (Wickham et al. 2019), readxl (Wickham and Bryan 2019), ggridges (Wilke 2021), magick (Ooms 2021), ggpubr (Kassambara 2020), gt (Iannone et al. 2021), knitr (Xie 2021) and rmarkdown (Allaire et al. 2021; Xie et al. 2020).

tidyverse package is an opinionated collection of following R packages: ggplot2 (Wickham 2016), dplyr (Wickham et al. 2021), tidyr (Wickham 2021a), readr (Wickham and Hester 2021), purrr (Henry and Wickham 2020), tibble (Müller and Wickham 2021), stringr (Wickham 2019) and forcats (Wickham 2021b). R code was provided with this paper as a supplementary document for reproducibility purposes (Marwick 2017).

Results

Top compounds in terms of their effects on percent change in average lifespan of diverse organisms collectively

Using a curated database of lifespan-extending drugs and compounds (DrugAge, http://genomics.senescence.info/drugs/) (Barardo et al. 2017), we ordered different compounds in terms of percent changes in the average lifespan in diverse organisms to which these drugs were given/applied, from highest to lowest. We found that aspirin [acetylsalicylic acid, a nonsteroidal anti-inflammatory drug (NSAID)] resulted in the highest percent increase in average lifespan

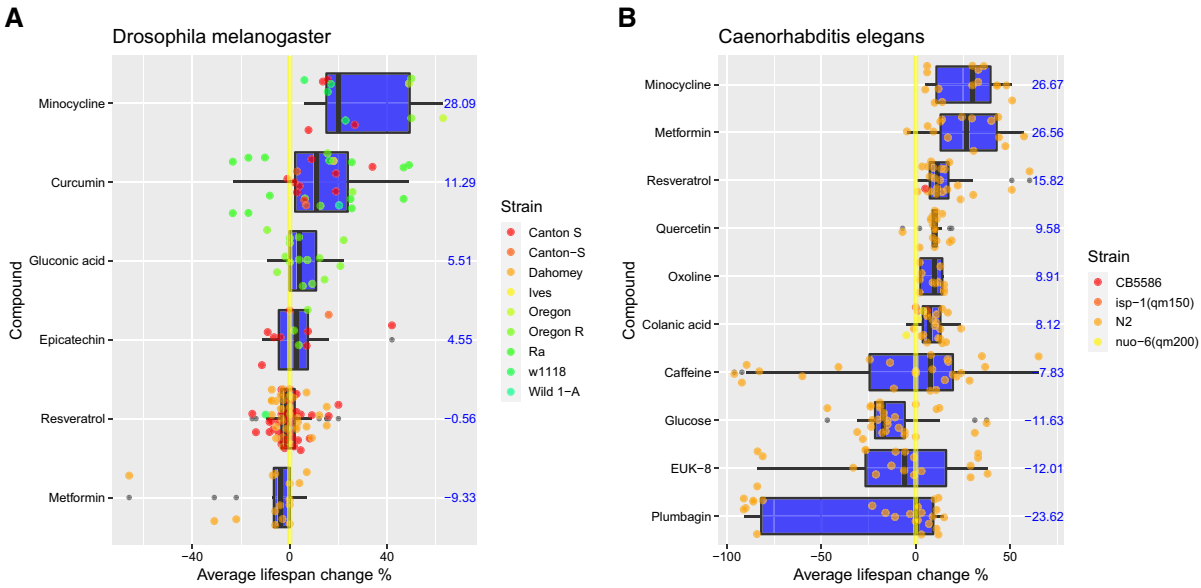


Fig. 2 The most effective compounds in terms of their effect on average lifespan change in *D. melanogaster* (**A**) and *C. elegans* (**B**). Top compounds resulting in the highest percent increase in average lifespan for *D. melanogaster* (left) and *C. elegans* (right), when data from different studies or experimental setups were combined for each compound per organism. Yellow vertical line indicates no change (0%) in average lifespan. Legend shows the color code for each strain. Values in blue at the end of *x* axis for every *y* value indicate mean percent change in average lifespan for each compound in that model organism. Compounds were ordered as the compound which caused the highest percent increase in average lifespan given at the top of plot (minocycline for both species)

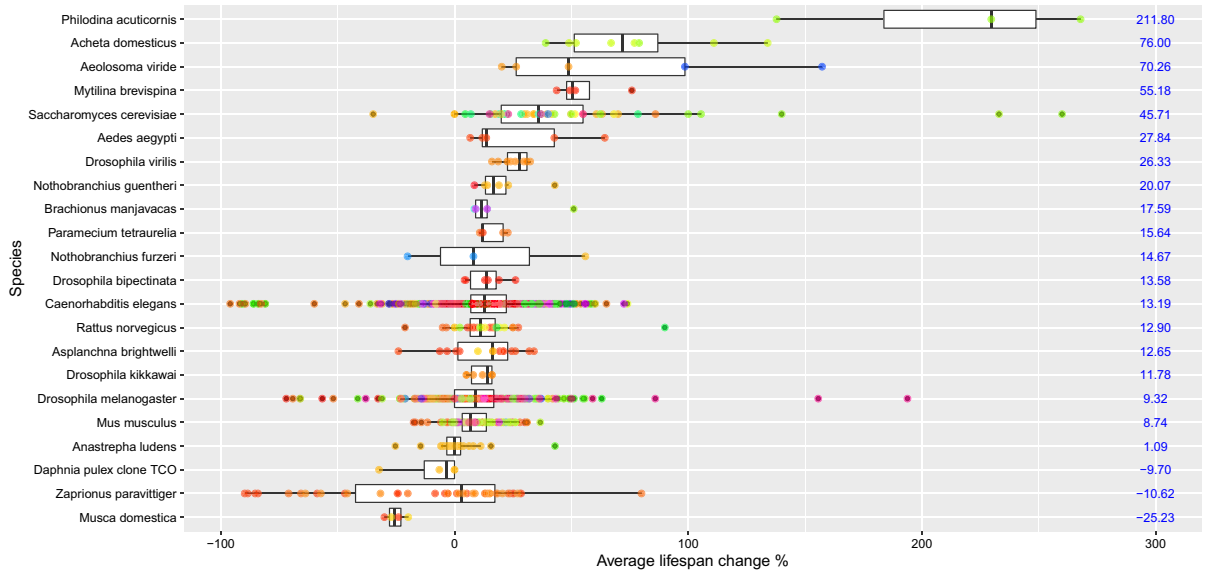


Fig. 3 Species whose lifespan can be extended the most by compounds with aging-related properties. Organisms whose average lifespan can be manipulated to the highest percentages by the application of compounds. Species were ordered as the species whose lifespan can be extended the most given at the top of the plot. Values in blue at the end of *x* axis for every *y* value indicate mean percent change in average lifespan for each species. Colored data points indicate different data which were obtained from different studies or experimental setups (different compound concentration, etc.). Each color represents different compound

among other compounds, when the effect of each compound on different organisms were combined (Fig. 1; here, please note that every compound were tested on the different sets of organisms). Aspirin led to a 52.01% increase in average in lifespan in tested organisms, followed by minocycline (+ 27.30%), *N*-acetyl cysteine (+ 17.93%), nordihydroguaiaretic acid (+ 17.65%) and rapamycin (+ 15.66%) (Fig. 1, bottom plot). Aspirin at certain concentrations caused more than 100% increase in *A. domesticus* (house cricket) (Fig. 1, top plot).

Although the percentage of average lifespan change caused by certain compounds such as vitamin E, colanic acid and oxoline showed a unimodal distribution (distributions with one clear peak); the percentage of average lifespan change caused by some compounds such as aspirin, metformin and plumbagin displayed a multimodal distribution [distributions with distinct peaks (local maxima)] (Fig. 1, bottom plot). Multimodal distribution observed for these compounds might be due to the differential effect of a particular compound on the average lifespan of different organisms such as in aspirin, or due to the differential effect of a particular compound in the same organisms at different concentrations or at experimental conditions (different studies) such as in EUK-8 and plumbagin (Fig. 1). Within compounds included in this dataset (also, we only included compounds with more than 10 different data points in the analysis, and filtered out others), plumbagin resulted in the highest decrease in average lifespan (− 23.62%) when data from different studies/experimental conditions were combined, followed by sodium hypophosphite (− 16.67%) and EUK-8 ((Salen)manganese(III) chloride) (− 12.01%) (Fig. 1). Please note that all the data for some compounds (including plumbagin, sodium hypophosphite and EUK-8) come from experiments performed on the same model organisms (Fig. 1, top plot, points with the same color).

We also summarized the modes of action of these compounds in terms of lifespan extension (Table 1); however, this list shows only some of the possible mechanisms responsible for the changes in the lifespan. It should also be noted that some of these proposed mechanisms might be species-specific, meaning that a compound might extend lifespan through different pathways in two different organisms. The concept of hormesis in terms of longevity-extending drugs was also discussed below.

Table 1 Some of the possible modes of action of longevity-extending compounds included in the present study

Compound	Possible modes of action to increase longevity	References
Aspirin	Autophagy (by mimicking caloric-restriction, by inhibiting acetyltransferase EP300), metabolism	Castoldi et al. (2018, 2020), Pietrocola et al. (2018a, b) Huang et al. (2017), Song et al. (2017), Wan et al. (2013)
Minocycline	SIRT1 activation; reduced protein aggregation due to preferential attenuation of the translation of highly translated mRNAs; lower concentration of nascent aggregation-prone proteins, leading to a relative increase in protein-folding capacity; higher activity of superoxide dismutase (SOD) and lower levels of nitric oxide (NO), hydrogen peroxide (H_2O_2) and mitochondrial malondialdehyde (MDA) (i.e. decreased lipid peroxidation)	Wu et al. (2020), Solis et al. 2018, Mora et al. (2013, 2014), Bonilla et al. (2012)
N-acetyl cysteine	Free radical scavenger; increased expression and activity of catalase, glutathione peroxidase and glutathione *S*-transferase (GST) (key enzymes to fend off reactive oxygen species (ROS) assaults); increased resistance to oxidative stress, heat stress, and UV irradiation	Brack et al. (1997), Niraula and Kim (2019), Savion et al. (2018), Oh et al. (2015)
Nordihydroguaiaretic acid	Inhibition of p300 and activation of autophagy; reduced hypothalamic inflammation in a sex-specific manner; augmented immunoproteasome function; altered energy homeostasis; potent reducing agent	Tezil et al. (2019), Sadagurski et al. (2017), Pickering et al. (2015), Spindler et al. (2015), Richie et al. (1986)
Rapamycin	Reduced translation errors/increased fidelity of protein synthesis; blockade of mTOR signaling; reduced tumor burden; increased autophagy and proteostasis; decreased mitochondrial ROS production at complex I, decreased oxidative stress, lower accumulation of mtDNA fragments inside nuclear DNA and lower lipofuscin levels	Martinez-Miguel et al. (2016, 2021), Ehninger et al. (2014), Saxton and Sabatini (2017), Kim et al. (2011), Vilchez et al. (2014)
Vitamin E	Antioxidant action; decrease in MDA and increase in catalase and peroxidase activities; decreased glucotoxic effects; inhibition of lipid peroxidation	Driver and Georgeou (2003), Kakkar et al. (1996), Schlotterer et al. (2020), Sakamoto et al. (2020)
Curcumin	Blockade of alcohol-induced damage to longevity and DNA methylation; protection against neurodegeneration; enhanced superoxide dismutase (SOD) activity, decreased malondialdehyde (MDA) and lipofuscin levels (i.e. reduced oxidative stress); increased SIRT1 activity	Rasmussen et al. (2021), Cheng et al. (2021), Zia et al. (2021), Iside et al. (2020), Chen et al. (2018), Seong et al. (2015)
Metformin	Improved nutrient sensing; enhanced autophagy and intercellular communication; protection against macromolecular damage; delayed stem cell aging; modulation of mitochondrial function; regulation of transcription; lower telomere attrition and senescence	Kulkarni et al. (2020)
Colanic acid	Protection of intestinal mitochondria from stress-induced hyper-fragmentation; regulation of mitochondrial dynamics and unfolded protein response (UPRmt)	Hartsough et al. (2020), Han et al. (2017)
Oxoline	Through stress hormesis mechanisms	Hunt et al. (2011)

Table 1 continued

Compound	Possible modes of action to increase longevity	References
Tannic acid	Amino acid metabolism; through TGF-beta and the p38 MAPK pathways; through DAF-12; mimicking calorie restriction and hormetic properties; through mitogen-activated protein kinase kinase SEK-1 (SAPK/ERK kinase)	Pietsch et al. (2012), Saul et al. (2010, 2011)
Rhodiola rosea	Increased stress resistance; induction of translocation of the DAF-16 into the nucleus, suggesting a reprogramming of transcriptional activities leading the synthesis of proteins functioning in stress resistance (such as the chaperone HSP-16); high level of antioxidant capacity	Wiegant et al. (2009), Shen et al. (2013)
Gluconic acid	Removal of hydroxyl radicals	Massie and Williams (1979)
Epicatechin	Stimulation of stress response mechanisms via the insulin/IGF-1 signaling pathway; reduced oxidative damage	Proshkina et al. (2016), Ayuda-Durán et al. (2019)
Resveratrol	Sirtuin activation; enhanced induction of mitophagy mediators; induction of mitonuclear protein imbalance and mitochondrial unfolded protein response; modulation of the expression of pro- and anti-apoptotic factors; neutralization of free radical species; chelation of redox-active transition metal ions and prevention of protein aggregation	Bonkowski and Sinclair (2016), Varghese et al. (2020), Houtkooper et al. (2013), Yessenkyzy et al. (2020), Lagouge et al. (2006)
Quercetin	Oxidative stress resistance (lower levels of reactive oxygen species, glutathione oxidation, protein carbonylation and lipid peroxidation); through metabolome; through TGF-beta signaling, insulin-like signaling and p38 MAPK pathway; improved neuroinflammation	Belinha et al. (2007), Pietsch et al. (2012), Gómez-Linton et al. (2019), Li et al. (2021), Kampkötter et al. (2008)
Caffeine	Protection against acute oxidative stress; promotion of proteostasis through induction of the heat shock response; scavenging of free radicals; resistance to proteotoxic stress	Li et al. (2019), Brunquell et al. (2018), Czachor et al. (2020), Sutphin et al. (2012)
Butylated hydroxyanisole	Increased catalase activity; reduced MDA content; reduced the levels of hepatic DNA damage; ROS suppression	Bains et al. (1998), Lawson and Stohs (1985), Ro et al. (2014), Stohs et al. (1986)
Glucose	Enhanced intestinal barrier integrity; via sirtuin and insulin signaling; modulation of immunity	Galenza and Foley (2020), Shintani et al. (1999), Galenza et al. (2016)
EUK-8	Mimicking superoxide dismutase (SOD); resistance to the oxidative stress-inducing agent, paraquat and to thermal stress	Sampayo et al. (2003)
Sodium hypophosphite	Increased catalase activity, alterations in peroxidase activity	Wadhwa and Sharma (1987), Wadhwa et al. (1988)
Plumbagin	Through stress hormesis mechanisms	Hunt et al. (2011)

The most effective compounds in terms of their effect on percent change in average lifespan, for *D. melanogaster* and *C. elegans*

Next, we identified compounds which are most effective in terms of their impact on average lifespan in two model organisms, for which the largest sample sizes are available in the dataset, namely, *D. melanogaster* and *C. elegans*. We found that minocycline is the most effective compound for both species among other compounds, in terms of lifespan extension (Fig. 2). This compound increased lifespan in *D. melanogaster* 28.09% in average, and in *C. elegans* 26.67% in average, when data from different studies

were combined (Fig. 2). For *D. melanogaster*, the second most effective compound for extending average lifespan is curcumin (+ 11.29%), followed by gluconic acid (+ 5.51%), whereas for *C. elegans*, the second most effective compound is metformin (+ 26.56), followed by resveratrol (+ 15.82%) and quercetin (+ 9.58%), again when data from different studies for each compound were analyzed collectively (Fig. 2). Although metformin and resveratrol were found to extend average lifespan in *C. elegans*, resveratrol had no effect on average lifespan (− 0.56%) and metformin decreased average lifespan around 10% in *D. melanogaster*, highlighting species-specific effects of certain compounds in terms of their impact on average lifespan (Fig. 2). However, glucose, EUK-8 and plumbagin was found to decrease lifespan in *C. elegans* (in average, − 11.63%, − 12.01% and − 23.62%, respectively), when all the data points from multiple sources were combined (Fig. 2).

Species whose lifespan can be extended the most by compounds with aging-related properties

To identify which species' lifespan can be extented the most by treatment with available aging-related compounds, we grouped data by species (also filtered out species with less than or equal to 2 data points), then ordered species in terms of lifespan extention due to the applications of compounds, and found that the lifespan of *P. acuticornis* (a species of freshwater bdelloid rotifers) can be extented the most, 211.80%, compared to the other species studied (Fig. 3). We showed that lifespan of *A. domesticus* (house cricket) can be extended by 76% in average (the second highest), that of *A. viride* (an asexually reproducing annelid/segmented worm) by 70.26%, that of *M. brevispina* (a rotifer) by 55.18% and that of *S. cerevisiae* (yeast) by 45.71% in average (Fig. 3). Therefore, these species can be considered as organisms whose lifespan can be most easily manipulated by the application of certain drugs, i.e. species most prone to manipulations by aging-related compounds.

Discussion

The treatment of the general aging population with geroprotectors, compounds that delay aging, was hypothesized to provide numerous benefits to the society, including a reduction in the prevalence of some age-related diseases or a delay in the onset of these diseases including cancer (Janssens and Houtkooper 2020). Many compounds that extend lifespan in model organisms have been identified to date, and the number of studies in this research area has been accelerating at an unprecedented rate, mostly due to the more common use of short-lived model organisms, the development of novel high-throughput technologies and new computational drug screening approaches (Janssens and Houtkooper 2020; Stroustrup et al. 2013; Carretero et al. 2015; Janssens et al. 2019; Calvert et al. 2016; Petrascheck et al. 2007; Ye et al. 2014). However, studies collectively analyzing data from these studies which were performed on different model organisms or at distinct experimental conditions are highly limited. Therefore, there is a need to combine all the data reported in all these studies and to analyze these data collectively in a broader perspective, in order to gain novel insights on the effect of lifespan-extending compounds on the lifespan of model organisms. These studies will help to increase the translatability of these compounds from model organisms to the clinic (Moskalev et al. 2016; de Magalhães 2014).

In this study, we first identified top compounds in terms of their effects on the percent change in the average lifespan of diverse organisms, by combining data from multiple studies performed using each compound on different sets of organisms. We found that aspirin increases the average lifespan the most, when data from multiple organisms are collectively analyzed, followed by minocycline, *N*-acetyl cysteine, nordihydroguaiaretic acid and rapamycin. Here, it should be noted that data for each compound is based on different sets of organisms; for some compounds, data is even based on different studies performed using a single species. By combining data for different species altogether per compound, we tried to get an idea on the average effect of particular compounds on the lifespan of model organisms in a species-independent manner. This is of importance since compounds with high effect on lifespan even when data from different species were combined, might have higher translatability to other species including humans. These compounds might be prioritized to be studied in other species. For instance, the health improving effects of aspirin depend on autophagy, at least in

mice, since these effects were observed only in autophagy-competent mice but not in two different models of genetic autophagy-deficiency (Castoldi et al. 2020). Since autophagy mechanism is also present in *A. domesticus* for which aspirin caused the highest increase in lifespan in this study, it can be speculated that organisms with active autophagy might potentially benefit from aspirin in terms of lifespan extension (Rost-Roszkowska et al. 2010). Compared to compounds which works through more species-specific mechanisms, compounds that stimulate evolutionarily more common processes might extend lifespan in a broader set of organisms, from worms to humans. Thus, these compounds can be more likely to be translated to the clinic.

Many of the studied lifespan-extending compounds seem to work by the process of hormesis which is described as the collection of evolutionarily conserved adaptive responses of biological systems (a cell or an entire organism) to moderate environmental or internal challenges through which the system enhances its functionality and/or tolerance against more severe future challenges, meaning that prior exposure to low (sublethal) doses of an insult protects from a higher, normally harmful or lethal dose of the same insult in the future (Calabrese and Mattson 2017; Rattan and Demirovic 2009; Cornelius et al. 2013; Le Bourg 2009; Calabrese et al. 2015, 2019; López-Martínez and Hahn 2014; Rattan 2018). For this reason, the concentration of a particular compound used in aging studies matters, due to the presence of specific hormetic dose responses of that drug in diverse organisms. However, since we focused on the effects of lifespan-extending compounds on multiple species in the present study, we could not study the concentration-dependent effects of these compounds in these species due to low sample sizes in terms of concentration. Most studies reported the use of specific concentrations of a compound; therefore, longevity data for a range of concentrations of a particular compound are mostly not available, restricting the analysis of dose responses in the majority of species. As shown in Table 1, many studies reported that certain compounds may extend longevity through stress-response hormesis mechanisms, in which sublethal exposure to a compound induces a response that results in stress resistance and ultimately in extended lifespan.

Different methods of application of these longevity-extending compounds to various species might also influence species-specific effects of these compounds in terms of lifespan extension, at least to a certain extent. For instance, *C. elegans* might be given bacteria containing the compound, or organisms living in water can be treated by the addition of the compound into water, or mice can be treated either by the addition of compound to its food or drinking water. Therefore, the effect of a particular compound on lifespan in different species might be influenced by the way it is given to that species, since these mediums (for instance, nematode growth medium or mice food) might alter the biological properties of that compound, its exposure to ambient temperature and moisture before it is taken up, and also change the final concentration of that compound available for the organism. This also complicates the cross-species analysis of a lifespan-extending compound. Although our understanding of the effects of these different methods of application of these longevity-extending compounds on longevity (if any) is highly limited, potential influence of these variables on longevity must be kept in mind when performing a cross-species analysis of lifespan-extending compounds.

We also identified compounds which are most effective in terms of extending average lifespan in *D. melanogaster* and *C. elegans*, the two most commonly studied model organisms in aging research, by combining available data from different studies. We found that minocycline (a second-generation tetracycline with anti-inflammatory properties) resulted in the highest increase (more than 25%) in average lifespan in both organisms, among other compounds studied, when data from multiple resources were collectively analyzed. Solis et al. showed that minocycline reduces protein aggregation by decreasing mRNA translation by ribosomes in the cytoplasm, preferentially attenuating the translation of highly translated mRNAs specifically, in *C. elegans* (Solis et al. 2018). Authors proposed that minocycline extends *C. elegans* lifespan, since it lowers the concentration of newly synthesized aggregation-prone proteins, leading to a relative enhancement of protein-folding capacity without the need to activate protein-folding pathways (Solis et al. 2018). They also reported that minocycline attenuates mRNA translation even in human cells (Solis et al. 2018). Thus, the inhibitory effect of minocycline on the translation of highly expressed,

aggregation prone proteins might not be specific to *C. elegans*, it might also be functioning in other organisms as evolutionarily distant as humans, due to the high conservation of translation machinery between these species. This might explain, at least in part, the fact that minocycline extend average lifespan the most in both *C. elegans* and *D. melanogaster*, and that minocycline results in the second highest increase in average lifespan following aspirin, among all other compounds, when all species are included in the analysis.

Furthermore, we identified species whose lifespan can be extended the most by compounds with lifespan-extending properties. We found that lifespans of top 5 species, namely, *P. acuticornis*, *A. domesticus*, *A. viride*, *M. brevispina* and *S. cerevisiae* can be extended by 211.80%, 76%, 70.26%, 55.18% and 45.71% in average, respectively. The lifespan of *P. acuticornis* (a rotifer) can be extended at a much higher percentage, compared to other species, more than two fold in average, by the application of compounds (Poeggeler et al. 2010). Why lifespan of *P. acuticornis* can be manipulated the most, among all organisms studied, is currently not known. However, this observation points that rotifer species (*M. brevispina* is also a rotifer) can be more commonly used in aging research due to the fact that their lifespans might be increased to relatively higher levels by compounds, thus enabling and simplifying the study of lifespan-extending molecules in model organisms (Snare et al. 2013; Gribble and Welch 2013; Gribble 2021; Lee et al. 2018; Bock et al. 2019). Further research is needed to better understand the extension of lifespan in rotifers (Snell 2014; Snell et al. 2015).

We recently studied Chordata species with exceptional longevity among taxa and the evolution of longer lifespans in chordates using another curated database from the same group (AnAge database) (Berkel and Cacan 2021; de Magalhães and Costa 2009; Tacutu et al. 2018). We believe that this type of big data compilations with high quality content from multiple resources, curated by researchers will help us to gain deeper insights in the biology of aging and lifespan, and also to translate findings in model organisms to humans (Budovksy et al. 2013; Avelar et al. 2020). Datasets with even larger sample sizes and with data for more diverse organisms will provide a better understanding of aging, which is previously not quite possible. However, it should be noted that both species-specific and the pan-species mechanisms of ageing were reported in many previous studies; and these set the limits for cross-species extrapolation in terms of longevity, for example from model organisms to humans (Rattan 2020). Mechanistic details of lifespan-extending interventions in model organisms might be worked to infer their applicability to humans; since, for instance, a drug which manipulates a certain pathway in a model organism to extend lifespan might fail to do so in humans, and thus a different drug should be evaluated and used to manipulate that particular pathway for the same purpose. Therefore, considering the certain limitations of model systems, findings based on studies performed on species other than humans might be carefully evaluated before attempting to translate these findings to human aging.

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Data availability Data used in the present study was obtained from DrugAge database (http://genomics.senescence.info/drugs/) [Build 3 (09/07/2019)] (Barardo et al. 2017).

Code availability R code used in the analysis was provided as a supplementary material.

Declarations

Conflict of interest Authors declare no conflicts of interest.

References

Allaire JJ, Xie Y, McPherson J, Luraschi J, Ushey K, Atkins A, Wickham H, Cheng J, Chang W, Iannone R (2021) rmarkdown: dynamic documents for R. R package version 2.10. https://rmarkdown.rstudio.com

Avelar RA, Ortega JG, Tacutu R, Tyler EJ, Bennett D, Binetti P, Budovsky A, Chatsirisupachai K, Johnson E, Murray A, Shields S, Tejada-Martinez D, Thornton D, Fraifeld VE, Bishop CL, de Magalhães JP (2020) A multidimensional systems biology analysis of cellular senescence in aging and disease. Genome Biol 21(1):91. https://doi.org/10.1186/s13059-020-01990-9

Ayuda-Durán B, González-Manzano S, Miranda-Vizuete A, Dueñas M, Santos-Buelga C, González-Paramás AM (2019) Epicatechin modulates stress-resistance in *C. elegans* via insulin/IGF-1 signaling pathway. PLoS ONE 14(1):e0199483. https://doi.org/10.1371/journal.pone.0199483

Bains JS, Garg SK, Sharma SP (1998) Effect of butylated hydroxyanisole on catalase activity and malondialdehyde

content in aging *Zaprionus paravittiger* (diptera). Gerontology 44(5):262–266. https://doi.org/10.1159/000022022

Barardo D, Thornton D, Thoppil H, Walsh M, Sharifi S, Ferreira S, Anžič A, Fernandes M, Monteiro P, Grum T, Cordeiro R, De-Souza EA, Budovsky A, Araujo N, Gruber J, Petrascheck M, Fraifeld VE, Zhavoronkov A, Moskalev A, de Magalhães JP (2017) The DrugAge database of aging-related drugs. Aging Cell 16(3):594–597. https://doi.org/10.1111/acel.12585

Belinha I, Amorim MA, Rodrigues P, de Freitas V, Moradas-Ferreira P, Mateus N, Costa V (2007) Quercetin increases oxidative stress resistance and longevity in *Saccharomyces cerevisiae*. J Agric Food Chem 55(6):2446–2451. https://doi.org/10.1021/jf063302e

Berkel C, Cacan E (2021) Analysis of longevity in Chordata identifies species with exceptional longevity among taxa and points to the evolution of longer lifespans. Biogerontology 22(3):329–343. https://doi.org/10.1007/s10522-021-09919-w

Bock MJ, Jarvis GC, Corey EL, Stone EE, Gribble KE (2019) Maternal age alters offspring lifespan, fitness, and lifespan extension under caloric restriction. Sci Rep 9(1):3138. https://doi.org/10.1038/s41598-019-40011-z

Bonilla E, Contreras R, Medina-Leendertz S, Mora M, Villalobos V, Bravo Y (2012) Minocycline increases the life span and motor activity and decreases lipid peroxidation in manganese treated *Drosophila melanogaster*. Toxicology 294(1):50–53. https://doi.org/10.1016/j.tox.2012.01.016

Bonkowski MS, Sinclair DA (2016) Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds. Nat Rev Mol Cell Biol 17(11):679–690. https://doi.org/10.1038/nrm.2016.93

Brack C, Bechter-Thüring E, Labuhn M (1997) N-acetylcysteine slows down ageing and increases the life span of *Drosophila melanogaster*. Cell Mol Life Sci 53(11–12):960–966. https://doi.org/10.1007/pl00013199

Brunquell J, Morris S, Snyder A, Westerheide SD (2018) Coffee extract and caffeine enhance the heat shock response and promote proteostasis in an HSF-1-dependent manner in *Caenorhabditis elegans*. Cell Stress Chaperones 23(1):65–75. https://doi.org/10.1007/s12192-017-0824-7

Budovsky A, Craig T, Wang J, Tacutu R, Csordas A, Lourenço J, Fraifeld VE, de Magalhães JP (2013) LongevityMap: a database of human genetic variants associated with longevity. Trends Genet 29(10):559–560. https://doi.org/10.1016/j.tig.2013.08.003

Calabrese EJ, Mattson MP (2017) How does hormesis impact biology, toxicology, and medicine? NPJ Aging Mech Dis 3:13. https://doi.org/10.1038/s41514-017-0013-z

Calabrese EJ, Dhawan G, Kapoor R, Iavicoli I, Calabrese V (2015) What is hormesis and its relevance to healthy aging and longevity? Biogerontology 16(6):693–707. https://doi.org/10.1007/s10522-015-9601-0

Calabrese EJ, Agathokleous E, Kapoor R, Kozumbo WJ, Rattan SIS (2019) Re-analysis of herbal extracts data reveals that inflammatory processes are mediated by hormetic mechanisms. Chem Biol Interact 314:108844. https://doi.org/10.1016/j.cbi.2019.108844

Calvert S, Tacutu R, Sharifi S, Teixeira R, Ghosh P, de Magalhães JP (2016) A network pharmacology approach reveals new candidate caloric restriction mimetics in *C. elegans*. Aging Cell 15(2):256–66. https://doi.org/10.1111/acel.12432

Carretero M, Gomez-Amaro RL, Petrascheck M (2015) Pharmacological classes that extend lifespan of *Caenorhabditis elegans*. Front Genet 6:77. https://doi.org/10.3389/fgene.2015.00077

Castoldi F, Pietrocola F, Maiuri MC, Kroemer G (2018) Aspirin induces autophagy *via* inhibition of the acetyltransferase EP300. Oncotarget 9(37):24574–24575. https://doi.org/10.18632/oncotarget.25364

Castoldi F, Humeau J, Martins I, Lachkar S, Loew D, Dingli F, Durand S, Enot D, Bossut N, Chery A, Aprahamian F, Demont Y, Opolon P, Signolle N, Sauvat A, Semeraro M, Bezu L, Baracco EE, Vacchelli E, Pol JG, Lévesque S, Bloy N, Sica V, Maiuri MC, Kroemer G, Pietrocola F (2020) Autophagy-mediated metabolic effects of aspirin. Cell Death Discov 6(1):129. https://doi.org/10.1038/s41420-020-00365-0

Chen Y, Liu X, Jiang C, Liu L, Ordovas JM, Lai CQ, Shen L (2018) Curcumin supplementation increases survival and lifespan in Drosophila under heat stress conditions. BioFactors 44(6):577–587. https://doi.org/10.1002/biof.1454

Cheng J, Wang H, Bartlett M, Stevenson D, Pan Y, Ho MS, Ren Y (2021) Antioxidant blend of curcumin and broccoli seed extract exhibits protective effect on neurodegeneration and promotes *Drosophila* lifespan. ASN Neuro. https://doi.org/10.1177/17590914211015033

Cornelius C, Perrotta R, Graziano A, Calabrese EJ, Calabrese V (2013) Stress responses, vitagenes and hormesis as critical determinants in aging and longevity: mitochondria as a "chi." Immun Ageing 10(1):15. https://doi.org/10.1186/1742-4933-10-15

Czachor J, Miłek M, Galiniak S, Stępień K, Dżugan M, Mołoń M (2020) Coffee extends yeast chronological lifespan through antioxidant properties. Int J Mol Sci 21(24):9510. https://doi.org/10.3390/ijms21249510

de Magalhães JP (2014) Why genes extending lifespan in model organisms have not been consistently associated with human longevity and what it means to translation research. Cell Cycle 13(17):2671–2673. https://doi.org/10.4161/15384101.2014.950151

de Magalhães JP, Costa J (2009) A database of vertebrate longevity records and their relation to other life-history traits. J Evol Biol 22(8):1770–1774. https://doi.org/10.1111/j.1420-9101.2009.01783.x

Driver C, Georgeou A (2003) Variable effects of vitamin E on Drosophila longevity. Biogerontology 4(2):91–95. https://doi.org/10.1023/a:1023347803932

Ehninger D, Neff F, Xie K (2014) Longevity, aging and rapamycin. Cell Mol Life Sci 71(22):4325–4346. https://doi.org/10.1007/s00018-014-1677-1

Galenza A, Foley E (2020) Glucose extends lifespan through enhanced intestinal barrier integrity in *Drosophila*. BioRxiv. https://doi.org/10.1101/2020.03.20.000968

Galenza A, Hutchinson J, Campbell SD, Hazes B, Foley E (2016) Glucose modulates Drosophila longevity and immunity independent of the microbiota. Biol Open 5(2):165–173. https://doi.org/10.1242/bio.015016

Gómez-Linton DR, Alavez S, Alarcón-Aguilar A, López-Diazguerrero NE, Konigsberg M, Pérez-Flores LJ (2019)

Some naturally occurring compounds that increase longevity and stress resistance in model organisms of aging. Biogerontology 20(5):583–603. https://doi.org/10.1007/s10522-019-09817-2

Gribble KE (2021) Brachionus rotifers as a model for investigating dietary and metabolic regulators of aging. Nutr Healthy Aging 6(1):1–15. https://doi.org/10.3233/NHA-200104

Gribble KE, Welch DB (2013) Life-span extension by caloric restriction is determined by type and level of food reduction and by reproductive mode in *Brachionus manjavacas* (Rotifera). J Gerontol A 68(4):349–358. https://doi.org/10.1093/gerona/gls170

Grolemund G, Wickham H (2017) R for data science. O'Reilly Media, Sebastopol

Han B, Sivaramakrishnan P, Lin CJ, Neve IAA, He J, Tay LWR, Sowa JN, Sizovs A, Du G, Wang J, Herman C, Wang MC (2017) Microbial genetic composition tunes host longevity. Cell 169(7):1249–1262.e13. https://doi.org/10.1016/j.cell.2017.05.036. Erratum in: Cell 2018;173(4):1058

Hartsough LA, Park M, Kotlajich MV, Lazar JT, Han B, Lin CJ, Musteata E, Gambill L, Wang MC, Tabor JJ (2020) Optogenetic control of gut bacterial metabolism to promote longevity. Elife 9:e56849. https://doi.org/10.7554/eLife.56849

Henry L, Wickham H (2020) purrr: functional programming tools. R package version 0.3.4. https://CRAN.R-project.org/package=purrr

Holtze S, Gorshkova E, Braude S, Cellerino A, Dammann P, Hildebrandt TB, Hoeflich A, Hoffmann S, Koch P, Terzibasi Tozzini E, Skulachev M, Skulachev VP, Sahm A (2021) Alternative animal models of aging research. Front Mol Biosci 8:660959. https://doi.org/10.3389/fmolb.2021.660959

Houtkooper RH, Mouchiroud L, Ryu D, Moullan N, Katsyuba E, Knott G, Williams RW, Auwerx J (2013) Mitonuclear protein imbalance as a conserved longevity mechanism. Nature 497(7450):451–457. https://doi.org/10.1038/nature12188

Huang XB, Mu XH, Wan QL, He XM, Wu GS, Luo HR (2017) Aspirin increases metabolism through germline signalling to extend the lifespan of *Caenorhabditis elegans*. PLoS ONE 12(9):e0184027. https://doi.org/10.1371/journal.pone.0184027

Hunt PR, Son TG, Wilson MA, Yu QS, Wood WH, Zhang Y, Becker KG, Greig NH, Mattson MP, Camandola S, Wolkow CA (2011) Extension of lifespan in *C. elegans* by naphthoquinones that act through stress hormesis mechanisms. PLoS ONE 6(7):e21922. https://doi.org/10.1371/journal.pone.0021922

Iannone R, Cheng J, Schloerke B (2021) gt: easily create presentation-ready display tables. R package version 0.3.1. https://CRAN.R-project.org/package=gt

Iside C, Scafuro M, Nebbioso A, Altucci L (2020) SIRT1 activation by natural phytochemicals: an overview. Front Pharmacol 11:1225. https://doi.org/10.3389/fphar.2020.01225

Janssens GE, Houtkooper RH (2020) Identification of longevity compounds with minimized probabilities of side effects. Biogerontology 21(6):709–719. https://doi.org/10.1007/s10522-020-09887-7

Janssens GE, Lin XX, Millan-Ariño L, Kavšek A, Sen I, Seinstra RI, Stroustrup N, Nollen EAA, Riedel CG (2019) Transcriptomics-based screening identifies pharmacological inhibition of Hsp90 as a means to defer aging. Cell Rep 27(2):467-480.e6. https://doi.org/10.1016/j.celrep.2019.03.044

Kakkar R, Bains JS, Sharma SP (1996) Effect of vitamin E on life span, malondialdehyde content and antioxidant enzymes in aging *Zaprionus paravittiger*. Gerontology 42(6):312–321. https://doi.org/10.1159/000213809

Kampkötter A, Timpel C, Zurawski RF, Ruhl S, Chovolou Y, Proksch P, Wätjen W (2008) Increase of stress resistance and lifespan of *Caenorhabditis elegans* by quercetin. Comp Biochem Physiol B 149(2):314–323. https://doi.org/10.1016/j.cbpb.2007.10.004

Kassambara A (2020) ggpubr: 'ggplot2' based publication ready plots. R package version 0.4.0. https://CRAN.R-project.org/package=ggpubr

Kim J, Kundu M, Viollet B, Guan KL (2011) AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 13(2):132–141. https://doi.org/10.1038/ncb2152

Kulkarni AS, Gubbi S, Barzilai N (2020) Benefits of metformin in attenuating the hallmarks of aging. Cell Metab 32(1):15–30. https://doi.org/10.1016/j.cmet.2020.04.001

Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J (2006) Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 127(6):1109–1122. https://doi.org/10.1016/j.cell.2006.11.013

Lawson T, Stohs S (1985) Changes in endogenous DNA damage in aging mice in response to butylated hydroxyanisole and oltipraz. Mech Ageing Dev 30(2):179–185. https://doi.org/10.1016/0047-6374(85)90006-5

Le Bourg E (2009) Hormesis, aging and longevity. Biochim Biophys Acta 1790(10):1030–1039. https://doi.org/10.1016/j.bbagen.2009.01.004

Lee MC, Park JC, Yoon DS, Han J, Kang S, Kamizono S, Om AS, Shin KH, Hagiwara A, Lee JS (2018) Aging extension and modifications of lipid metabolism in the monogonont rotifer *Brachionus koreanus* under chronic caloric restriction. Sci Rep 8(1):1741

Li H, Roxo M, Cheng X, Zhang S, Cheng H, Wink M (2019) Pro-oxidant and lifespan extension effects of caffeine and related methylxanthines in *Caenorhabditis elegans*. Food Chem X 1:100005. https://doi.org/10.1016/j.fochx.2019.100005

Li H, Chen FJ, Yang WL, Qiao HZ, Zhang SJ (2021) Quercetin improves cognitive disorder in aging mice by inhibiting NLRP3 inflammasome activation. Food Funct 12(2):717–725. https://doi.org/10.1039/d0fo01900c

López-Martínez G, Hahn DA (2014) Early life hormetic treatments decrease irradiation-induced oxidative damage, increase longevity, and enhance sexual performance during old age in the Caribbean fruit fly. PLoS ONE 9(1):e88128. https://doi.org/10.1371/journal.pone.0088128

Martínez-Cisuelo V, Gómez J, García-Junceda I, Naudí A, Cabré R, Mota-Martorell N, López-Torres M, González-Sánchez M, Pamplona R, Barja G (2016) Rapamycin

reverses age-related increases in mitochondrial ROS production at complex I, oxidative stress, accumulation of mtDNA fragments inside nuclear DNA, and lipofuscin level, and increases autophagy, in the liver of middle-aged mice. Exp Gerontol 83:130–138. https://doi.org/10.1016/j.exger.2016.08.002

Martinez-Miguel VE, Lujan C, Espie-Caullet T, Martinez-Martinez D, Moore S, Backes C, Gonzalez S, Galimov ER, Brown AEX, Halic M, Tomita K, Rallis C, von der Haar T, Cabreiro F, Bjedov I (2021) Increased fidelity of protein synthesis extends lifespan. Cell Metab. https://doi.org/10.1016/j.cmet.2021.08.017

Marwick B (2017) Rrtools: creates a reproducible research compendium. https://github.com/benmarwick/rrtools

Massie HR, Williams TR (1979) Increased longevity of *Drosophila melanogaster* with lactic and gluconic acids. Exp Gerontol 14(3):109–115. https://doi.org/10.1016/0531-5565(79)90025-1

Mora M, Medina-Leendertz SJ, Bonilla E, Terán RE, Paz MC, Arcaya JL (2013) Minocycline, but not ascorbic acid, increases motor activity and extends the life span of *Drosophila melanogaster*. Invest Clin 54(2):161–170

Mora M, Bonilla E, Medina-Leendertz S, Bravo Y, Arcaya JL (2014) Minocycline increases the activity of superoxide dismutase and reduces the concentration of nitric oxide, hydrogen peroxide and mitochondrial malondialdehyde in manganese treated *Drosophila melanogaster*. Neurochem Res 39(7):1270–1278. https://doi.org/10.1007/s11064-014-1309-z

Moskalev A, Chernyagina E, Tsvetkov V, Fedintsev A, Shaposhnikov M, Krut'ko V, Zhavoronkov A, Kennedy BK (2016) Developing criteria for evaluation of geroprotectors as a key stage toward translation to the clinic. Aging Cell 15(3):407–415. https://doi.org/10.1111/acel.12463

Müller K, Wickham H (2021) tibble: simple data frames. R package version 3.1.3. https://CRAN.R-project.org/package=tibble

Niraula P, Kim MS (2019) N-Acetylcysteine extends lifespan of Drosophila via modulating ROS scavenger gene expression. Biogerontology 20(4):533–543. https://doi.org/10.1007/s10522-019-09815-4

Oh SI, Park JK, Park SK (2015) Lifespan extension and increased resistance to environmental stressors by N-acetyl-L-cysteine in *Caenorhabditis elegans*. Clinics (Sao Paulo) 70(5):380–386. https://doi.org/10.6061/clinics/2015(05)13

Ooms J (2021) magick: advanced graphics and image-processing in R. R package version 2.7.3. https://CRAN.R-project.org/package=magick

Petrascheck M, Ye X, Buck LB (2007) An antidepressant that extends lifespan in adult *Caenorhabditis elegans*. Nature 450(7169):553–556. https://doi.org/10.1038/nature05991

Pickering AM, Lehr M, Miller RA (2015) Lifespan of mice and primates correlates with immunoproteasome expression. J Clin Invest 125(5):2059–2068. https://doi.org/10.1172/JCI80514

Pietrocola F, Castoldi F, Maiuri MC, Kroemer G (2018a) Aspirin-another caloric-restriction mimetic. Autophagy 14(7):1162–1163. https://doi.org/10.1080/15548627.2018.1454810

Pietrocola F, Castoldi F, Markaki M, Lachkar S, Chen G, Enot DP, Durand S, Bossut N, Tong M, Malik SA, Loos F, Dupont N, Mariño G, Abdelkader N, Madeo F, Maiuri MC, Kroemer R, Codogno P, Sadoshima J, Tavernarakis N, Kroemer G (2018b) Aspirin recapitulates features of caloric restriction. Cell Rep 22(9):2395–2407. https://doi.org/10.1016/j.celrep.2018.02.024

Pietsch K, Saul N, Swain SC, Menzel R, Steinberg CE, Stürzenbaum SR (2012) Meta-analysis of global transcriptomics suggests that conserved genetic pathways are responsible for quercetin and tannic acid mediated longevity in *C. elegans*. Front Genet 3:48. https://doi.org/10.3389/fgene.2012.00048

Poeggeler B, Sambamurti K, Siedlak SL, Perry G, Smith MA, Pappolla MA (2010) A novel endogenous indole protects rodent mitochondria and extends rotifer lifespan. PLoS ONE 5(4):e10206. https://doi.org/10.1371/journal.pone.0010206

Proshkina E, Lashmanova E, Dobrovolskaya E, Zemskaya N, Kudryavtseva A, Shaposhnikov M, Moskalev A (2016) Geroprotective and radioprotective activity of quercetin, (-)-epicatechin, and ibuprofen in *Drosophila melanogaster*. Front Pharmacol 7:505. https://doi.org/10.3389/fphar.2016.00505

R Core Team (2020) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/

Rasmussen EMK, Seier KL, Pedersen IK, Kreibich C, Amdam GV, Münch D, Dahl JA (2021) Screening bioactive food compounds in honey bees suggests curcumin blocks alcohol-induced damage to longevity and DNA methylation. Sci Rep 11(1):19156. https://doi.org/10.1038/s41598-021-98614-4

Rattan SIS (2018) Biogerontology: research status, challenges and opportunities. Acta Biomed 89(2):291–301. https://doi.org/10.23750/abm.v89i2.7403

Rattan SIS (2020) Naive extrapolations, overhyped claims and empty promises in ageing research and interventions need avoidance. Biogerontology 21(4):415–421. https://doi.org/10.1007/s10522-019-09851-0

Rattan SI, Demirovic D (2009) Hormesis can and does work in humans. Dose Response 8(1):58–63. https://doi.org/10.2203/dose-response.09-041.Rattan

Richie JP Jr, Mills BJ, Lang CA (1986) Dietary nordihydroguaiaretic acid increases the life span of the mosquito. Proc Soc Exp Biol Med 183(1):81–85. https://doi.org/10.3181/00379727-183-42389

Ro SH, Nam M, Jang I, Park HW, Park H, Semple IA, Kim M, Kim JS, Park H, Einat P, Damari G, Golikov M, Feinstein E, Lee JH (2014) Sestrin2 inhibits uncoupling protein 1 expression through suppressing reactive oxygen species. Proc Natl Acad Sci USA 111(21):7849–7854. https://doi.org/10.1073/pnas.1401787111

Rost-Roszkowska MM, Poprawa I, Chachulska-Zymełka A (2010) Apoptosis and autophagy in the midgut epithelium of *Acheta domesticus* (Insecta, Orthoptera, Gryllidae). Zool Sci 27(9):740–745. https://doi.org/10.2108/zsj.27.740

Sadagurski M, Cady G, Miller RA (2017) Anti-aging drugs reduce hypothalamic inflammation in a sex-specific

manner. Aging Cell 16(4):652–660. https://doi.org/10.1111/acel.12590

Sakamoto T, Maebayashi K, Tsunoda Y, Imai H (2020) Inhibition of lipid peroxidation during the reproductive period extends the lifespan of *Caenorhabditis elegans*. J Clin Biochem Nutr 66(2):116–123. https://doi.org/10.3164/jcbn.19-51

Sampayo JN, Olsen A, Lithgow GJ (2003) Oxidative stress in *Caenorhabditis elegans*: protective effects of superoxide dismutase/catalase mimetics. Aging Cell 2(6):319–326. https://doi.org/10.1046/j.1474-9728.2003.00063.x

Saul N, Pietsch K, Menzel R, Stürzenbaum SR, Steinberg CE (2010) The longevity effect of tannic acid in *Caenorhabditis elegans*: disposable soma meets hormesis. J Gerontol A 65(6):626–635. https://doi.org/10.1093/gerona/glq051

Saul N, Pietsch K, Stürzenbaum SR, Menzel R, Steinberg CE (2011) Diversity of polyphenol action in *Caenorhabditis elegans*: between toxicity and longevity. J Nat Prod 74(8):1713–1720. https://doi.org/10.1021/np200011a

Savion N, Levine A, Kotev-Emeth S, Bening Abu-Shach U, Broday L (2018) S-allylmercapto-N-acetylcysteine protects against oxidative stress and extends lifespan in *Caenorhabditis elegans*. PLoS ONE 13(3):e0194780. https://doi.org/10.1371/journal.pone.0194780

Saxton RA, Sabatini DM (2017) mTOR signaling in growth, metabolism, and disease. Cell 169(2):361–371. https://doi.org/10.1016/j.cell.2017.03.035. Erratum for: Cell 2017;168(6):960–976

Schlotterer A, Masri B, Humpert M, Krämer BK, Hammes HP, Morcos M (2020) Sulforaphane and vitamin E protect from glucotoxic neurodegeneration and lifespan reduction in *C. elegans*. Exp Clin Endocrinol Diabetes. https://doi.org/10.1055/a-1158-9248

Seong KM, Yu M, Lee KS, Park S, Jin YW, Min KJ (2015) Curcumin mitigates accelerated aging after irradiation in Drosophila by reducing oxidative stress. Biomed Res Int 2015:425380. https://doi.org/10.1155/2015/425380

Shen B, Truong J, Helliwell R, Govindaraghavan S, Sucher NJ (2013) An in vitro study of neuroprotective properties of traditional Chinese herbal medicines thought to promote healthy ageing and longevity. BMC Complement Altern Med 13:373. https://doi.org/10.1186/1472-6882-13-373

Shintani T, Sakoguchi H, Yoshihara A, Izumori K, Sato M (2019) D-Allose, a stereoisomer of D-glucose, extends the lifespan of *Caenorhabditis elegans* via sirtuin and insulin signaling. J Appl Glycosci 66(4):139–142. https://doi.org/10.5458/jag.jag.JAG-2019_0010

Snare DJ, Fields AM, Snell TW, Kubanek J (2013) Lifespan extension of rotifers by treatment with red algal extracts. Exp Gerontol 48(12):1420–1427. https://doi.org/10.1016/j.exger.2013.09.007

Snell TW (2014) Rotifers as models for the biology of aging. Int Rev Hydrobiol 99(1–2):84–95. https://doi.org/10.1002/iroh.201301707

Snell TW, Johnston RK, Gribble KE, Mark Welch DB (2015) Rotifers as experimental tools for investigating aging. Invertebr Reprod Dev 59(1):5–10. https://doi.org/10.1080/07924259.2014.925516

Solis GM, Kardakaris R, Valentine ER, Bar-Peled L, Chen AL, Blewett MM, McCormick MA, Williamson JR, Kennedy B, Cravatt BF, Petrascheck M (2018) Translation attenuation by minocycline enhances longevity and proteostasis in old post-stress-responsive organisms. Elife 7:e40314. https://doi.org/10.7554/eLife.40314

Song C, Zhu C, Wu Q, Qi J, Gao Y, Zhang Z, Gaur U, Yang D, Fan X, Yang M (2017) Metabolome analysis of effect of aspirin on Drosophila lifespan extension. Exp Gerontol 95:54–62. https://doi.org/10.1016/j.exger.2017.04.010

Spindler SR, Mote PL, Lublin AL, Flegal JM, Dhahbi JM, Li R (2015) Nordihydroguaiaretic acid extends the lifespan of drosophila and mice, increases mortality-related tumors and hemorrhagic diathesis, and alters energy homeostasis in mice. J Gerontol A 70(12):1479–1489. https://doi.org/10.1093/gerona/glu190

Stohs SJ, Lawson TA, Anderson L, Bueding E (1986) Effects of oltipraz, BHA, ADT and cabbage on glutathione metabolism, DNA damage and lipid peroxidation in old mice. Mech Ageing Dev 37(2):137–145. https://doi.org/10.1016/0047-6374(86)90071-0

Stroustrup N, Ulmschneider BE, Nash ZM, López-Moyado IF, Apfeld J, Fontana W (2013) The *Caenorhabditis elegans* lifespan machine. Nat Methods 10(7):665–670. https://doi.org/10.1038/nmeth.2475

Sutphin GL, Bishop E, Yanos ME, Moller RM, Kaeberlein M (2012) Caffeine extends life span, improves healthspan, and delays age-associated pathology in *Caenorhabditis elegans*. Longev Healthspan 1:9. https://doi.org/10.1186/2046-2395-1-9

Tacutu R, Thornton D, Johnson E, Budovsky A, Barardo D, Craig T, Diana E, Lehmann G, Toren D, Wang J, Fraifeld VE, de Magalhães JP (2018) Human ageing genomic resources: new and updated databases. Nucleic Acids Res 46(D1):D1083–D1090. https://doi.org/10.1093/nar/gkx1042

Taormina G, Ferrante F, Vieni S, Grassi N, Russo A, Mirisola MG (2019) Longevity: lesson from model organisms. Genes (Basel) 10(7):518. https://doi.org/10.3390/genes10070518

Tezil T, Chamoli M, Ng CP, Simon RP, Butler VJ, Jung M, Andersen J, Kao AW, Verdin E (2019) Lifespan-increasing drug nordihydroguaiaretic acid inhibits p300 and activates autophagy. NPJ Aging Mech Dis 5:7. https://doi.org/10.1038/s41514-019-0037-7

Varghese N, Werner S, Grimm A, Eckert A (2020) Dietary mitophagy enhancer: a strategy for healthy brain aging? Antioxidants (Basel) 9(10):932. https://doi.org/10.3390/antiox9100932

Vilchez D, Saez I, Dillin A (2014) The role of protein clearance mechanisms in organismal ageing and age-related diseases. Nat Commun 5:5659. https://doi.org/10.1038/ncomms6659

Wadhwa R, Sharma SP (1987) Studies on catalase in ageing *Zaprionus paravittiger* (Diptera) with special reference to an antioxidant feeding. Mech Ageing Dev 40(2):139–147. https://doi.org/10.1016/0047-6374(87)90013-3

Wadhwa R, Kaur M, Sharma SP (1988) An antioxidant induced alterations in peroxidase activity in ageing *Zaprionus paravittiger* (Diptera). Mech Ageing Dev 45(3):277–283. https://doi.org/10.1016/0047-6374(88)90008-5

Wan QL, Zheng SQ, Wu GS, Luo HR (2013) Aspirin extends the lifespan of *Caenorhabditis elegans* via AMPK and DAF-16/FOXO in dietary restriction pathway. Exp

Gerontol 48(5):499–506. https://doi.org/10.1016/j.exger.2013.02.020
Wickham H (2016) ggplot2: elegant graphics for data analysis. Springer-Verlag, New York
Wickham H (2019) stringr: simple, consistent wrappers for common string operations. R package version 1.4.0. https://CRAN.R-project.org/package=stringr
Wickham H (2021a) tidyr: tidy messy data. R package version 1.1.3. https://CRAN.R-project.org/package=tidyr
Wickham H (2021b) forcats: tools for working with categorical variables (factors). R package version 0.5.1. https://CRAN.R-project.org/package=forcats
Wickham H, Bryan J (2019) readxl: read excel files. R package version 1.3.1. https://CRAN.R-project.org/package=readxl
Wickham H, Hester J (2021) readr: read rectangular text data. R package version 2.0.1. https://CRAN.R-project.org/package=readr
Wickham H et al (2019) Welcome to the tidyverse. J Open Source Softw 4(43):1686. https://doi.org/10.21105/joss.01686
Wickham H, François R, Henry L, Müller K (2021) dplyr: a grammar of data manipulation. R package version 1.0.7. https://CRAN.R-project.org/package=dplyr
Wiegant FA, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA (2009) Plant adaptogens increase lifespan and stress resistance in *C. elegans*. Biogerontology 10(1):27–42. https://doi.org/10.1007/s10522-008-9151-9
Wilke CO (2021) ggridges: ridgeline plots in 'ggplot2'. R package version 0.5.3. https://CRAN.R-project.org/package=ggridges
Wu LH, Huang BR, Lai SW, Lin C, Lin HY, Yang LY, Lu DY (2020) SIRT1 activation by minocycline on regulation of microglial polarization homeostasis. Aging (Albany NY) 12(18):17990–18007. https://doi.org/10.18632/aging.103542
Xie Y (2021) knitr: a general-purpose package for dynamic report generation in R. R package version 1.33
Xie Y, Dervieux C, Riederer E (2020) R Markdown Cookbook. Chapman and Hall/CRC. ISBN 9780367563837. https://bookdown.org/yihui/rmarkdown-cookbook
Ye X, Linton JM, Schork NJ, Buck LB, Petrascheck M (2014) A pharmacological network for lifespan extension in *Caenorhabditis elegans*. Aging Cell 13(2):206–215. https://doi.org/10.1111/acel.12163
Yessenkyzy A, Saliev T, Zhanaliyeva M, Masoud AR, Umbayev B, Sergazy S, Krivykh E, Gulyayev A, Nurgozhin T (2020) Polyphenols as caloric-restriction mimetics and autophagy inducers in aging research. Nutrients 12(5):1344. https://doi.org/10.3390/nu12051344
Zia A, Farkhondeh T, Pourbagher-Shahri AM, Samarghandian S (2021) The role of curcumin in aging and senescence: molecular mechanisms. Biomed Pharmacother 134:111119. https://doi.org/10.1016/j.biopha.2020.111119