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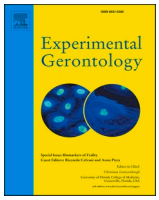

Review

Dietary antioxidants and lifespan: Relevance of environmental conditions, diet, and genotype of experimental models

Alfonso Varela-López [a], José M. Romero-Márquez [a], María D. Navarro-Hortal [a], César L. Ramirez-Tortosa [b], Maurizio Battino [c,d], Tamara Y. Forbes-Hernández [a], José L. Quiles [a,e,f,*]

[a] Department of Physiology, Institute of Nutrition and Food Technology "José Mataix", Biomedical Research Center, University of Granada, Avda del Conocimiento s/n, Parque Tecnologico de la Salud, Armilla, Granada 18016, Spain
[b] UGC de Anatomía Patológica Hospital San Cecilio de Granada, Granada, Spain
[c] Department of Clinical Sciences, Polytechnic University of Marche, 60131 Ancona, Italy
[d] International Joint Research Laboratory of Intelligent Agriculture and Agri-products Processing, Jiangsu University, Zhenjiang 212013, China
[e] Research Group on Foods, Nutritional Biochemistry and Health, Universidad Europea del Atlántico, Isabel Torres, 21, 39011 Santander, Spain
[f] Research and Development Functional Food Centre (CIDAF), Health Science Technological Park, Avenida del Conocimiento 37, 18016 Granada, Spain

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ABSTRACT

The rise of life expectancy in current societies is not accompanied, to date, by a similar increase in healthspan, which represents a great socio-economic problem. It has been suggested that aging can be manipulated and then, the onset of all age-associated chronic disorders can be delayed because these pathologies share age as primary underlying risk factor. One of the most extended ideas is that aging is consequence of the accumulation of molecular damage. According to the oxidative damage theory, antioxidants should slow down aging, extending lifespan and healthspan. The present review analyzes studies evaluating the effect of dietary antioxidants on lifespan of different aging models and discusses the evidence on favor of their antioxidant activity as anti-aging mechanisms. Moreover, possible causes for differences between the reported results are evaluated.

1. Introduction

Life expectancy has been substantially improved worldwide over the last century which has been largely attributed to advances in public health practice, education and medicine (Vaiserman and Lushchak, 2017). It is generally assumed that if such demographic trend will continue then about 20 % of the global population will be older than 60 years by 2050 (Kennedy and Pennypacker, 2014). However, this rise of life expectancy has not been accompanied, to date, by a similar increase in healthspan (Hung et al., 2011). Aging increases the risk for common chronic pathologies including type 2 diabetes mellitus, cardiovascular diseases, osteoporosis, neurodegenerative diseases, cancer and other metabolic-related diseases. Consequently, with the rapid aging of the population in most of modern societies, the prevalence of aging-related pathological conditions will increase, representing a great socio-economic problem (Beard and Bloom, 2015; Harper, 2014; Lopreite and Mauro, 2017). Notwithstanding, the cost pressure related to population aging can be minimized by the development of efficient health interventions, such as disease-prevention and health-promotion programs that target major causes of morbidity in the elderly which allow to the population stays healthy until a very old age (Lopreite and Mauro, 2017). It has been suggested that aging can be manipulated and if aging is modulated, the onset of all age-associated chronic disorders can be delayed because these pathologies share age as primary underlying risk

Abbreviations: AMPK, AMP-activated protein kinase; CAT, catalase; CNC, cap 'n' collar; CoQ, coenzyme Q; EGCG, epigallocatechin gallate; GFP, green fluorescence protein; HO-1, hemeoxygenase-1; IGF, insulin-like growth factor; MitoQ, mitoquinone; *Mth*, methuselah; Nrf, nuclear respiratory factor; PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1 α; SKN-1, protein skinhead-1; FOXO, Forkhead box O; NF-κB, nuclear factor κB; ROS, reactive oxygen species; SAMP, senescence-accelerated mouse prone; SAMR, senescence-accelerated mouse resistant; SIRT1, sirtuin 1; SIR-2, sirtuin 2; SOD, superoxide dismutase; TOR, target of rapamycin.

* Corresponding author at: Department of Physiology, Institute of Nutrition and Food Technology "José Mataix", Biomedical Research Center, University of Granada, Avda del Conocimiento s/n, Parque Tecnologico de la Salud, Armilla, Granada 18016, Spain.
E-mail address: jlquiles@ugr.es (J.L. Quiles).

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factor (Austad, 2016; Sierra and Kohanski, 2017). Therefore, extension of the healthy life expectancy by slowing aging process is the most efficient way to combat aging-related chronic illnesses and disabling conditions representing serious medical, social and economic issue in modern societies. In this sense, interventions through changes in dietary patterns or using dietary supplements or nutraceuticals specifically targeted at common mechanisms of aging, might be an effective way to prevent and fight against age-related pathologies.

2. Biology of aging and antioxidants

Aging is an unavoidable, universal, biological phenomenon affecting all multicellular organisms (with few apparent exceptions). Although it has been traditionally regarded as 'natural' and consequently unpreventable process, most present-day evolutionary theories postulate that aging has arisen as a by-product of fundamental evolutionary processes and does not have any specific function (Lemaître et al., 2015). Consequently, it might be manipulated, and age-associated senescence may be regarded as a complex of pathophysiological processes that could be prevented, delayed or even reversed (Anton et al., 2005). Currently, the research attempted to enhance healthspan is focused primarily on slowing or postpone the biological processes underlying aging. This includes mitochondrial dysfunctions, impaired proteostasis and stem cell function and maintenance, deregulated sensing of cell energy status and growth pathways, cellular senescence, age-related decrease in stress resistance, as well as oxidative and inflammatory stress (Fontana et al., 2014; Kirkland, 2016; Niedernhofer et al., 2017). Identification of processes underlying aging and further development of interventions addressing these processes is apparently a challenging task considering the extreme complexity of aging-related processes. Different hypotheses have been put forward to explain the cellular and molecular mechanisms of aging. One of the most extended ideas is that aging is consequence of the accumulation of molecular damage (Brewer, 2010; Cefalu, 2011; Hughes and Reynolds, 2005; Rattan, 2012; Viña, 2019; Viña et al., 2007). Reactions of free radicals and other reactive oxygen species (ROS) are one of the main causes of such damage. The "Free Radical Theory of Aging" (Harman, 1956), now more commonly termed the oxidative damage theory of aging (Gladyshev, 2014; Kirkwood and Kowald, 2012), suggests that free radicals and other ROS, formed unavoidably in the course of metabolism and arising due to the action of various exogenous factors, damage biomolecules; and the accumulation of this damage is the cause of age-related diseases and aging (Barja, 2013). According to this theory, antioxidants should slow down aging and prolong lifespan and healthspan. This apparently obvious conclusion has stimulated enormous number of studies aimed at finding a relationship between levels of endogenous antioxidants and lifespan of various organisms on the effects of addition of exogenous antioxidants on the course of aging and lifespan of model organisms (Sadowska-Bartosz and Bartosz, 2014).

3. Antioxidants assayed in model organisms of aging: effects on lifespan and healthspan

Results from studies in model organisms on the supplementation with antioxidant vitamins and other antioxidants are divergent (Table 1). One of the first group of compounds present in foodstuff investigated in antiaging research were antioxidant vitamins that usually are firstly classified as liposoluble or hydrosoluble. The hydrosoluble vitamin C was not able to increase survival in *C. elegans* (Harrington and Harley, 1988). Likewise, D-erythroascorbic acid, the ascorbic acid homologue produced in the yeast, showed little effect on the replicative lifespan of wild-type yeast (Lam et al., 2010). In addition, vitamin supplementation for 9 months decreased lifespan in field vole (*Microtus agrestis*) (Selman et al., 2013). In fact, a review on effects of vitamin C on the lifespan of several multicellular model organisms including *C. elegans*, *D. melanogaster*, mice, rats, and guinea pigs, concluded that no consistent picture emerges from the summary of data since some studies demonstrated prolongation of lifespans and others showed no effect (Pallauf et al., 2013).

Regarding liposoluble vitamins, it has been reported that the vitamin E form α-tocopherol increased mean lifespan in *C. elegans* (Harrington and Harley, 1988; Ishii et al., 2004), and even in C57BL/6 (Banks et al., 2010), C3H/He and LAF1 mice (Blackett and Hall, 1981), although it had no effect in mice in another study (Morley and Trainor, 2001). However, in a different investigation, it was reported that γ-, but not α-tocopherol slightly extended mean lifespan in nematodes. Moreover, neither significantly affected lifespan in the flies *D. melanogaster* nor *Anastrepha ludens* (Zou et al., 2007). Again, vitamin E supplementation for 9 months showed a deleterious effect on *M. agrestis* lifespan (Selman et al., 2013). Similarly a review on the effects of vitamin E on lifespan in rotifers, *C. elegans*, *D. melanogaster*, and laboratory rodents suggested that there is no consistent beneficial effect, which corresponds to results of meta-analysis of mortality in human intervention studies (Ernst et al., 2013). Lastly, carotenoids also have been considered important antioxidant molecules regardless they are provitamins A, but their effects on lifespan have been little studied. Still, astaxanthin provided to pre-reproductive adult *C. elegans* extended the mean lifespans by about 16–30 % (Yazaki et al., 2011).

Additional lipid substances that act as coenzyme have been tested (Table 2). Lipoic acid has shown to decrease lifespan in SAMP8 mice (Farr et al., 2012) despite it was increased in *D. melanogaster* (Bauer et al., 2004). Exogenous ubiquinone, in the form of coenzyme Q $(CoQ)_{10}$, prolonged lifespan in *C. elegans* (Asencio et al., 2009) but in most of the studies, in both rats and mice, CoQ_{10} supplementation was ineffective for increasing lifespan (Lee et al., 2004; Lönnrot et al., 1995; Sohal et al., 2006). Importantly, according to the variety of used CoQ_{10} doses (ranged from 10 to 370 mg/Kg per day) and the duration of the different studies, the lack of effects on longevity seems, in many of these studies, not to depend on these conditions. Still, long-life dietary supplementation with the reduced form was able to slow aging in senescence-accelerated mouse prone 1 (SAMP1) in different studies (Tian et al., 2014; Yan et al., 2006). Interestingly, triptolide, a diterpenoid epoxide, that is a major active compound found in Thunder God Vine (*Tripterygium wilfordii*) added to the growth media lead to increased mean, but also maximum lifespans in *C. elegans* (S.-J. Kim, Beak, y Park 2017). Concerning peptides, it has been reported that carnosine increased mean lifespan in males, but it had no effect on females of *D. melanogaster* (Stvolinsky et al., 2010). Importantly, its derivative S,S-trolox-carnosine increased it in both, males and females (Stvolinsky et al., 2010).

Polyphenolic compounds such as curcumin and multiple flavonoids have received many attentions because their wide biological activities, especially as antioxidants. For this reason, it was not unexpected that many of them have been tested as potential anti-aging compounds (Table 3). The most studied molecules from this family of compounds have been resveratrol and curcumin. Resveratrol is a phytoalexin synthesized in many plants, such as peanuts, blueberries, pine nuts, and grapes, that stimulates cell defenses in plants protecting them against fungal infection and ultraviolet irradiation. Resveratrol at different concentrations added to a larval diet was able to extend adult longevity in *D. melanogaster* (Bauer et al., 2004; Chandrashekara and Shakarad, 2011), but did not extend normal life span in *C. elegans* (Chen et al., 2013). On the contrary, lifespan extension effects of resveratrol were conserved in the honeybee (*Apis mellifera*) (Rascón et al., 2012). Moreover, resveratrol increased locomotor activity in adult males of *D. melanogater* which would indicate a better neuroprotection (Chandrashekara and Shakarad, 2011). Interestingly, resveratrol supplements increased mean life expectancy and maximal life span in SAMP8 and in their control, the related strain SAMR1 at the same time that reduced cognitive impairment and showed a neuroprotective role decreasing the amyloid burden and reducing tau hyperphosphorylation (Porquet et al., 2013). Similarly, its glucoside polydatin (resveratrol-3-Oβ-mono-D-glucoside) also showed to increase *C. elegans* mean lifespan (Wen et al.,

Table 1
Main results from studies on the effects of vitamin supplementation on lifespan.

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
Vitamin C (unspecified form)	*Caenorhabditis elegans*					
	Wild-type Bristol N2 strain	80 μg/ml	Hatching	–	–	(Harrington and Harley, 1988).
Ascorbate	*Musca domestica*					
	Wild-type	0.5 %	NA	⇩	⇩	(Sohal et al., 1985)
	Wild-type	2.0 %	NA	⇩	⇩	(Sohal et al., 1985)
Ascorbic acid	*Caenorhabditis elegans*					
	Wild-type Bristol N2 strain	5 mM	Hatching	–	–	(Schulz et al., 2007)
	Wild-type Bristol N2 strain exposed to D-glucose (50 mM)	5 mM	Hatching	–	–	(Schulz et al., 2007)
	Drosophila melanogaster					
	Wild-type rosy^{+5} strain	0.02 mM	Hatching	–	NA	(Bahadorani et al., 2008)
		0.2 mM	Hatching	–	NA	
		2 mM	Hatching	–	NA	
		20 mM	Hatching	⇧	NA	
		100 mM	Hatching	⇩	NA	
	Wild-type Oregon R strain	10 mM	1 d	⇧	⇧	(Massie et al., 1991)
		100 mM	1 d	⇩	⇩	
		1 mM	Hatching	⇧	⇧	
		10 mM	Hatching	⇩	⇩	
		50 mM	Hatching	⇩	⇩	
		1 mM	Hatching	⇩	⇩	
		10 mM	Hatching	⇩	⇩	
		50 mM	Hatching	⇩	⇩	
	Wild-type Swedish C strain	1 mM	1 d	⇧	⇧	(Massie et al., 1991)
		10 mM	1 d	⇧	⇧	
		100 mM	1 d	⇩	⇩	
	Cavia porcellus					
	Dunkin Hartley strain	5 mg/kg of bw				(Davies et al., 1977)
	Mus musculus					
	C57BL/6J strain	50 mg/kg of bw	2 m	⇧	⇧	(Bezlepkin et al., 1996)
		50 mg/kg of bw	9 m	⇧	⇧	
		50 mg/kg of bw	16 m	⇧	⇧	
		50 mg/kg of bw	23 m	⇧	⇩	
		1.43 mg/kg of bw	37 d	⇧	⇧	(Massie et al., 2009)
	CD-1	920 mg/kg of diet (1.9 y)	9 m	–	NA	(Tappel et al., 1973)
	Rattus novergicus					
	Long Evans, active	2500 mg/kg of diet	3 m	⇧	NA	(Holloszy, 1998)
	Long Evans, sedentary	2500 mg/kg of diet	3 m	⇧	NA	(Holloszy, 1998)
Ascorbyl-2-polyphosphate	*Microtus agrestis*					
	Collected from a wild population remained in 22 + 2 °C	180 mg/kg	2 m	⇩	⇩	(Selman et al., 2013).
	Collected from a wild population transferred to the 7 + 2 °C	180 mg/kg	2 m	⇩	⇩	(Selman et al., 2013).
	Mus musculus					
	C57BL/6 J strain	180 mg/kg of diet	4 m	–	NA	(Selman et al., 2006)
Gamma -tocopherol	*Anastrepha ludens*					
		100 μg/ml	During adulthood	–	NA	(Zou et al., 2007)
	Caenorhabditis elegans					
	Fem-1 mutant	200 μg/ml	During adulthood	⇧	–	(Zou et al., 2007)
		20 μg/ml	During adulthood	⇧	–	(Zou et al., 2007)
	Drosophila melanogaster					
		20 μg/ml	During adulthood	–	NA	(Zou et al., 2007)
		100 μg/ml	During adulthood	–	NA	(Zou et al., 2007)
		200 μg/ml	During adulthood	⇩	NA	(Zou et al., 2007)
Gamma –tocopherol + α-tocopherol	*Caenorhabditis elegans*					
	Fem-1 mutant	20 μg/ml	During adulthood	–	–	(Zou et al., 2007) (Zou et al., 2007)
		200 μg/ml	During adulthood	–	–	
RRR-α-tocopherol	*Mus musculus*					
	Male	5000 μg/g	28 wk	⇧	⇧	(Navarro et al., 2005)
Tocotrienol mix	*Caenorhanditis elegans*					

(*continued on next page*)

Table 1 (*continued*)

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
	Wild-type Bristol N2 strain	8 μg/ml	Adult stage	⇧	NA	(Adachi and Ishii, 2000)
		80 μg/ml	Adult stage	⇧	NA	(Adachi and Ishii, 2000)
Vitamin C + vitamin E	*Caenorhanditis elegans*					
	Wild-type Bristol N2 strain	80 μg/ml + 200 μg/ml	Hatching	–	–	(Harrington and Harley, 1988).
Vitamin E (unspecified form)	*Drosophila melanogaster*					
		3 μg/ml	NA	–	NA	(Driver and Georgeou, 2003)
		20 μg/ml	NA	⇧	NA	
		100 μg/ml	NA	–	NA	
		200 μg/ml	NA	–	NA	
	Mus musculus					
	Balb/c strain	20 μg/g	Birth	–	–	(Morley and Trainor, 2001)
		400 μg/g	Birth	–	–	
		4000 μg/g	Birth	–	–	
α-Tocopherol	*Anastrepha ludens*					
		100 μg/ml	During adulthood	–	NA	(Zou et al., 2007)
	Caenorhabditis elegans					
	Fem-1 mutant	200 μg/ml	During adulthood	–	–	(Zou et al., 2007)
	Mev-1 mutant	400 μg/ml	L1 stage	–	NA	(Ishii et al., 2004)
	Wild-type Bristol N2 strain	200 μg/ml (3 d)	Hatching	⇧	–	(Harrington and Harley, 1988)
		100 μg/ml	Hatching	⇧	–	(Harrington and Harley, 1988)
		400 μg/ml	L1	⇧	NA	(Ishii et al., 2004)
		20 μg/ml	During adulthood	–	–	(Zou et al., 2007)
	Drosophila melanogaster					
		0.005 IU/ml	After hatching	–	–	(Bahadorani et al., 2008)
		0.05 IU/ml	After hatching	–	–	
		0.5 IU/ml	Hatching	–	–	
		5 IU/ml	Hatching	–	–	
		25 IU/ml	Hatching	–	–	
		20 μg/ml	During adulthood	–	NA	(Zou et al., 2007)
		100 μg/ml	During adulthood	–	NA	
		200 μg/ml	During adulthood	⇩	NA	
	Microtus agrestis					
	From a wild population remained in 22 + 2 °C	550 mg/kg	2 m	⇩	–	(Selman et al., 2013)
	From a wild population transferred to the 7 + 2 °C	550 mg/kg	2 m	⇩	–	(Selman et al., 2013)
	Musca domestica					
		0.5 %	NA	–	NA	(Sohal et al., 1985)
		2 %	NA	⇩	NA	(Sohal et al., 1985)
	Mus musculus					
	CH3/LAF1 strain	2500 μg/g	5 wk	NA	–	(Blackett and Hall, 1981)
	Rattus novergicus					
	Wistar strain, male	2000 μg/g	Weaning	–	–	(Porta et al., 1980)
	Zaprionus paravittiger					
		1 μg/ml	Birth	⇧	⇧	(Kakkar et al., 1996)
		5 μg/ml	Birth	⇧	⇧	
		10 μg/ml	Birth	⇧	⇧	
		25 μg/ml	Birth	⇩	⇩	
		50 μg/ml	Birth	⇩	⇩	
α-Tocopherol acetate	*Caenorhabditis elegans*					
	Wild-type Bristol N2 strain	80 μg/ml	Adult stage	–	NA	(Adachi and Ishii, 2000)
	Mus musculus					
	C57BL/6 strain	470 ppm	18 m	–	–	(Lipman et al., 1998)
	C3 strain, female	4400 μg/g	6.5 wk	–	–	(Ledvina and Hodáňová, 1980)
All-rac-α-tocopherol acetate	*Mus musculus*					
	MRL/lpr strain	50 μg/g	3 m	–	NA	(Hsieh and Lin, 2005)
		250 μg/g	3 m	⇧	NA	
		375 μg/g	3 m	⇩	NA	
		500 μg/g	3 m	⇩	NA	

Abbreviations and symbols: d: days; m: months; NA: not available; wk.: weeks; ⇧: statistically significant increase; ⇩ statistically significant decrease; –: not significant. Sex only was indicated if both sexes were not included.

Table 2
Main results from studies on the effects of Coenzyme Q (CoQ) and lipoic acid on lifespan.

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
Lipoic acid	*Drosophila melanogaster*					
	Canton-S strain	0.005 %	NA	⇧	–	(Bauer et al., 2004)
	Mus musculus					
	C57BL/6 × C3H (B6C3F 1), male, fed 98 kcal/wk. of the AIN-93 M diet	100 mg/kg of bw per day	14 m	–	–	(Lee et al., 2004)
	SAMP8 strain	100 mg/kg of bw per day	11 m	⇩	NA	(Farr et al., 2012)
Oxidized CoQ_{10}	*Caenorhabditis elegans*					
	Mev-1 mutant	150 μg/ml	L1 stage	⇧	NA	(Ishii et al., 2004)
		50 μg/ml	L1 stage	⇧	NA	
	Wild-type Bristol N2 strain	150 μg/ml	L1 stage	⇧	NA	(Ishii et al., 2004)
		50 μg/ml	L1 stage	⇧	NA	
	Mus musculus					
	SAMP1 strain	250 mg/kg per d	4 wk	–	NA	(Yan et al., 2006)
	SAMP1 strain	250 mg/kg per d	4 wk	–	NA	(Yan et al., 2006)
	C57BL/6, male, fed ad libitum	371 mg/kg of bw per day, from 3 m	3 m	–	NA	(Sohal et al., 2006)
	Rattus novergicus					
	Sprague-Dawley strain	125 mg/Kg of diet	Before birth	–	NA	(Lönnrot et al., 1995)
		250 mg/Kg of diet	Before birth	–	NA	
		50 mg/Kg of diet	Before birth	–	NA	
Reduced CoQ_{10}	*Mus musculus*					
	C57BL/6, male, fed ad libitum	93 mg/kg of bw per d	3 m	–	NA	(Sohal et al., 2006)
	SAMP1 strain	0.3 %	1 m	–	NA	(Tian et al., 2014)
		0.3 %	7 m	–	NA	
		0.3 %	13 m	–	NA	
	M. musculus, SAMR1 strain	250 mg/kg per d	4 wk	–	NA	(Yan et al., 2006)
		250 mg/kg per d	4 wk	–	NA	

Abbreviations and symbols: d: days; m: months; NA: not available; wk.: weeks; ⇧: statistically significant increase; ⇩ statistically significant decrease; –: not significant. Sex only was indicated if both sexes were not included.

2014). Resveratrol effects on different mammalian species, including humans, have been also extensively reviewed. A meta-analysis on the effect of resveratrol on survival using data from 19 published papers indicated that lifespan of the turquoise killifish was positively affected, but results were less clear for flies and nematodes, with an important variability found between the different studies (Hector et al., 2012). However, despite many studies have explored the role of resveratrol supplementation in aging, data on the effects of this molecule on longevity in healthy but non-obese mammals are rare (Marchal et al., 2013).

Curcumin is the main bioactive polyphenol of the yellow extract from turmeric *Curcuma longa*, which has been used widely as a spice, food additive, and a herbal medicine in Asia (Shen et al., 2013a). Numerous excellent narrative and systematic reviews describe how curcumin and/or its analogs have multiple anti-aging effects (Bahrami et al., 2021; Bielak-Zmijewska et al., 2019; Pulido-Moran et al., 2016; Vera-Ramirez et al., 2013; Zia et al., 2021). Curcumin at 1.0 (but not at 0.5 mg/g of media) increased male *D. melanogaster* mean lifespan in different assays (Lee et al., 2010; Shen et al., 2013b; Suckow and Suckow, 2006), although lifespan extension seemed to be gender-and genotype-specific (Lee et al., 2010). Many studies show that in mice, worms, yeasts, and flies, curcumin or its semi-synthetic derivatives or its combination with other nutraceuticals remarkably extend lifespan and promote healthy aging (Cheng et al., 2021; Zhou et al., 2021a, 2021b). Likewise, the curcumin metabolite, tetrahydrocurcumin added to the diet from the age of 13 months increased mean lifespan of male C57BL/6 mice. Moreover the 10 % longest survival was also significantly greater in mice treated with this compound which would suggest that this compound can be able to increase maximum lifespan of the model. Importantly, if mice started the treatment at 19th month of life, no significant difference from the control mice was found for either, mean or maximum lifespan (Shen et al., 2013a). Another important group of antioxidant compounds is the green tea catechins. These compounds have been reported to be more effective antioxidants than Vitamins C and E with important radical scavenger activities. It has been reported that catechin (Saul et al., 2009) and epigallocatechin gallate (EGCG) (Abbas and Wink, 2009) increased mean lifespan in *C. elegans*, but (−)-epicatechin had not effect on lifespan. Moreover EGCG failed to increase it in another study (Zhang et al., 2009). Notwithstanding, it also increased median lifespan in Wistar rats (Niu et al., 2013) and green tea polyphenols from the age of 13 months increased male C57BL/6 mice median lifespan (Kitani et al., 2007). Interestingly, EGCG at 1000 μM reduced lifespan in *C. elegans* despite life was extended with a lower concentration 200 μM. Nonetheless, combining high-dose EGCG with theanine reversed high-dose EGCG-induced lifespan reduction in *C. elegans* (Peng et al., 2021).

Other multiple polyphenols with reported biological activities have been assessed although the number of studies and models was much lower. Tyrosol (Cañuelo et al., 2012), caffeic acid, rosmarinic acid (Pietsch et al., 2011), ferulsinaic acid (Sayed, 2011), ferulic acid (Li et al., 2021), myricetin, kaempferol, naringenin (Grünz et al., 2012), and apple procyanidins (Sunagawa et al., 2011), increased lifespan in *C. elegans*. To the mentioned compounds it can be added quercetin (Grünz et al., 2012; Kampkötter et al., 2007; Surco-Laos et al., 2011) and its derivatives obtained by methylation after deglycosylation of the glycosides present in foodstuffs, isorhamnetin (quercetin 3′-*O*-methyl-ether) and tamarixetin (quercetin 4′-*O*-methylether) (Surco-Laos et al., 2011). Interestingly, Quercetin-3-O-glucoside at higher concentration (50–200 μM) even decreased mean and maximum lifespan in *C. elegans* despite the prolonging effect of lower concentrations (10 μM and 25 μM) (Dueñas et al., 2013).

Melatonin supplementation of *Paramecium tetraurelia* increased

Table 3
Main results from studies on the effects of resveratrol and derivatives on lifespan.

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
Polydatin	*Caenorhabditis elegans*					
	wild-type Bristol N2 strain	0.01 mM	L1 stage	⇧	NA	(Wen et al., 2014)
		0.1 mM	L1 stage	⇧	NA	
		1 mM	L1 stage	⇧	NA	
	Wild-type Bristol N2 strain exposed to 500 μM Cu^{2+} for 24 h	0.01 mM	L1 stage	⇧	NA	(Wen et al., 2014)
		0.1 mM	L1 stage	⇧	NA	
		1 mM	L1 stage	⇧	NA	
Resveratrol	*Apis mellifera*					
		130 μM	4 d	⇧	⇧	(Rascón et al., 2012)
		30 μM	4 d	⇧	⇧	
	under hyperoxia	130 μM	4 d	–	–	(Rascón et al., 2012)
		30 μM	4 d	–	–	
	Caenorhabditis elegans					
	Fem-1 mutant	65 μg/ml	Adult stage	–	NA	(Sunagawa et al., 2011)
	Mev-1 mutant	100 μM	Adult stage	–	NA	(Chen et al., 2013)
		200 μM	Adult stage	⇩	NA	
		50 μM	Adult stage	–	NA	
		65 μg/ml	Young adult	–	NA	(Sunagawa et al., 2011)
	Wild-type N2 Bristol strain	200 μM	Adult stage	⇧	NA	(Chen et al., 2013)
		100 μM	Adult stage	⇧	NA	
		50 μM	Adult stage	⇧	NA	
	Wild-type N2 Bristol strain in liquid S-medium	200 μM	Adult stage	–	NA	(Chen et al., 2013)
		100 μM	Adult stage	–	NA	
		50 μM	Adult stage	–	NA	
	Wild-type N2 Bristol strain under high-glucose treatment	200 μM	Adult stage	⇧	NA	(Chen et al., 2013)
		100 μM	Adult stage	–	NA	
		50 μM	Adult stage	⇧	NA	
	C. elegans, Sir-2.1 mutants	65 μg/ml	Adult stage	–	NA	(Sunagawa et al., 2011)
	Drosophila melanogaster					
	Caton-S strain	200 μM	NA	⇧	–	(Bauer et al., 2004)
	Male	800 mM	1 d	–	⇧	(Chandrashekara and Shakarad, 2011)
		200 mM	1 d	–	⇧	
		100 mM	1 d	–	⇧	
		50 mM	1 d	–	⇧	
		25 mM	1 d	–	⇧	
Trans-resveratrol	*Mus musculus*					
	SAMP8 strain	1 g/kg of diet	2 m	⇧	⇧	(Porquet et al., 2013)
	SAMR1 strain	1 g/kg of diet	2 m	⇧	⇧	(Porquet et al., 2013)

Abbreviations and symbols: d: days; m: months; NA: not available; wk.: weeks; ⇧: statistically significant increase; ⇩ statistically significant decrease; –: not significant. Sex only was indicated if both sexes were not included.

mean and maximum clonal lifespan (Thomas and Smith-Sonneborn, 1997). Melatonin increase lifespan in *D. melanogaster* (Izmaylov and Obukhova, 1999) and senescence-acceleration prone (SAMP)8 mice and even in the senescent resistant (SAMR1) strain (Rodríguez et al., 2008) (Table 4).

It has been argued that antioxidant mixtures, such as those found in natural products, are better than simple antioxidant formulas. This might be due to the synergism between antioxidants. It might be argued that more complex combinations of such agents might extend lifespan or health-span by more closely mimicking the complexity of micro-nutrients in fruits and vegetables, which appear to extend health-span and longevity (Table 5). Mean lifespan was extended in *D. melanogaster* treated with extract of aloe vera (Chandrashekara and Shakarad, 2011), black rice (Zuo et al., 2012), *Rhodiola rosea* (Rutledge et al., 2021), cocoa (Bahadorani and Hilliker, 2008), blueberry (Peng et al., 2012), orange, tangerine or grapefruit peel (Oboh et al., 2021). Similar findings were found in *C. elegans* treated with extracts from *Ginkgo biloba* leaves (Wu et al., 2002) or cranberry (Guha et al., 2014). Importantly, early-start intervention with cranberry extract has a more robust effect than late-start intervention on remaining lifespan (Guha et al., 2014). *Hericium erinaceus* mycelia extract and its bioactive compound erinacine A extended lifespan in *D. melanogaster* and SAMP8 mice (Li et al., 2019; Tsai et al., 2019). Likewise, a herb complex named KPG-7 containing *Thymus vulgaris*, *Rosmarinus officinalis*, *Curcuma longa*, *Foeniculum vulgare*, *Vitis vinifera*, silk protein, *Tarax acum officinale*, and *Eleutherococcus senticosus* extended lifespan and delayed aging in adult *C. elegans* (Moriwaki et al., 2013). Furthermore, locomotive activity was increased in *C. elegans* at 3 days of age following the treatment

Table 4
Main results of studies on melatonin effect on lifespan.

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
Melatonin	*Drosophila melanogaster*					
	wild type Canton-S strain	0.08 % w/w	Adult stage	⇧/⇩	NA	(Izmaylov and Obukhova, 1999)
	Mus musculus					
	SAMP8 strain	10 mg/kg of bw	1 m	⇧	⇧	(Rodríguez et al., 2008)
	SAMR1 strain	10 mg/kg of bw	1 m	⇧	⇧	(Rodríguez et al., 2008)

Abbreviations and symbols: bw: body weight; m: months; NA: not available; ⇧: statistically significant increase; ⇩ statistically significant decrease.

Table 5
Main results from studies on the effects of different mixtures on lifespan.

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
Aloe vera leaf extract	*Drosophila melanogaster*					
	Wild-type	5 ml/l	1 d	⇑	⇑	(Chandrashekara and Shakarad, 2011)
Apple polyphenols	*Caenorhabditis elegans*					
	Fem-1 mutants	100 μg/ml	Adult stage	⇑	NA	(Sunagawa et al., 2011)
	Wild-type N2 Bristol strain	100 μg/ml	Adult stage	⇑	NA	(Sunagawa et al., 2011)
	Sir-2.1 mutants	100 μg/ml	Adult stage	⇑	NA	(Sunagawa et al., 2011)
Black rice extract	*Drosophila melanogaster*					
	Wild-type Oregon R strain	10 mg/ml	NA	–	NA	(Zuo et al., 2012)
		30 mg/ml	NA	⇑	NA	
Blueberry extract	*Drosophila melanogaster*					
	Wild-type Oregon R strain	2 mg/ml	NA	–	–	(Peng et al., 2012)
		5 mg/ml	NA	⇑	–	
Bone Restore® plus K2	*Mus musculus*					
	+B6C3F1 strain, male	584 mg/kg of diet	12 m	⇑	NA	(Spindler et al., 2014)
Cocoa extract	*Drosophila melanogaster*					
	Wild-type *rosy*$^{+5}$ strain under hyperoxia	10 %	Adult stage	⇑	NA	(Bahadorani and Hilliker, 2008)
		5 %	Adult stage	⇑	NA	
	Wild-type *rosy*$^{+5}$ strain under normoxia	10 %	Adult stage	–	NA	(Bahadorani and Hilliker, 2008)
		5 %	Adult stage	⇑	NA	
Cranberry extract	*Caenorhabditis elegans*					
	Wild-type N2 Bristol strain	2 mg/ml	L4 stage	⇑	NA	(Guha et al., 2014)
		2 mg/ml	L4 stage	⇑	NA	
		2 mg/ml	L4 stage	⇑	NA	
		2 mg/ml	Before birth	⇑	NA	
		2 mg/ml	Before birth	⇑	NA	
		2 mg/ml	Before birth	⇑	NA	
Dietary Supplement	*Mus musculus*					
	C57BL/6J male × SJL female hybrids	4 g/kg of bw per day	2 m	–	NA	(Lemon et al., 2005)
	Transgenic growth hormone mice	4 g/kg of bw per day	2 m	⇑	NA	(Lemon et al., 2005)
Grapefruit peel extract	*Drosophila melanogaster*					
	W^{1118} strain	0.1 %	3–5 d	⇑	NA	(Oboh et al., 2021)
		1 %	3–5 d	⇑	NA	
H. erinaceus mycellia rich in Erinacine A	*Drosophila melanogaster*					
	Wild-type Canton-S strain	0.11 mg/ml	Adult stage	⇑	NA	(Li et al., 2019)
		0.35 mg/ml	Adult stage	⇑	NA	
		1.05 mg/ml	Adult stage	⇑	NA	
	Mus musculus					
	SAMP8 strain, female	108 mg/Kg of bw per day (13 d)	6 m	–	NA	(Li et al., 2019)
		215 mg/Kg of bw per day (13 d)	6 m	–	NA	
		431 mg/kg of bw per day (13 d)	6 m	⇑	NA	
	SAMP8 strain, male	108 mg/Kg of bw per day (13 d)	6 m	–	NA	(Li et al., 2019)
		431 mg/Kg of bw per day (13 d)	6 m	⇑	NA	
		215 mg/Kg of bw per day (13 d)	6 m	⇑	NA	
Juvenon® (Juvenon Inc.)	*Mus musculus*					
	B6C3F1 strain, male	3.74 g/kg of diet	12 m	–	NA	Spindler et al., 2014)
KPG-7 herb complex (KIPPO Sci. Ltd. Tokyo, Japan)	*Caenorhabditis elegans*					
	Fem-3 mutant	10 %	L1 stage	⇑	NA	(Moriwaki et al., 2013)
	Wild-type N2 Bristol strain	10 %	L1 stage	⇑	NA	(Moriwaki et al., 2013)
Lecithin, *G. biloba*, glucosamine HCl & garlic	*Mus musculus*					
	B6C3F1 strain, male	1.75 mg + 189 mg + 1.17 g + 2.1 g per kg of diet	12 m	–	NA	Spindler et al., 2014)
LGcombo	*Mus musculus*					

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Table 5 (*continued*)

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
	B6C3F1 strain, male	60.83 g	12 m	⇑	NA	(Spindler et al., 2014)
Life Extension Mix® (LEF)	*Mus musculus*					
	B6C3F1 strain, male	12.5 g/kg of diet	12 m	–	NA	Spindler et al., 2014)
LRcombo diet supplement	*Mus musculus*					
	B6C3F1 strain, male	27.8 g total/kg of diet	12 m	–	NA	Spindler et al., 2014)
Major royal-jelly proteins	*Drosophila melanogaster*					
	Wild-type Canton-S flies	1.25 %		⇑	–	(Xin et al., 2016)
		2.50 %		⇑	–	
		5.00 %		⇑	⇑	
Orange peel extract	*Drosophila melanogaster*					
	W^{1118} strain	0.1 %	3–5 d	⇑	NA	(Oboh et al., 2021)
		1 %	3–5 d	⇑	NA	(Oboh et al., 2021)
Ortho Core® (AOR)	*Mus musculus*					
	B6C3F1 strain, male	5.76 g/kg of diet	12 m	–	NA	Spindler et al., 2014)
Ortho Mind® (AOR)	*Mus musculus*					
	B6C3F1 strain, male	5.25 g/kg of diet	12 m	–	NA	Spindler et al., 2014)
R. damascena petal extract	*Drosophila melanogaster*					
	Outbred population selected for accelerated development	2 mg/ml	Adult stage	–	NA	(Rutledge et al., 2021)
	Outbred population selected for accelerated development fed apple-based diet	2 mg/ml	Adult stage	–	NA	(Rutledge et al., 2021)
	Outbred population selected for accelerated development fed banana-based diet	2 mg/ml	Adult stage	⇑	NA	(Rutledge et al., 2021)
R. rosea root extract	*Drosophila melanogaster*					
	Outbred population selected for accelerated development	25 mg/ml	Adult stage	⇑	NA	(Rutledge et al., 2021)
R. rosea root extract & R. damascena petal extract combination	*Drosophila melanogaster*					
	Outbred population selected for accelerated development	25 + 2 mg/ml	Adult stage	⇑	NA	(Rutledge et al., 2021)
Royal jelly	*Caenorhabditis elegans*					
	Wild-type N2 Bristol strain	1 μg/ml	Adult stage	–	NA	(Honda et al., 2011)
		10 μg/ml	Adult stage	⇑	NA	
		100 μg/ml	Adult stage	–	NA	
	Mus musculus					
	C3H/HeJ strain, male	0.6 mg/Kg of bw per day	6 wk	–	NA	(Inoue et al., 2003)
		6 mg/Kg of bw per day	6 wk	⇑	NA	
		60 mg/Kg of bw per day	6 wk	⇑	NA	
Royal jelly ethanol soluble faction	*Caenorhabditis elegans*					
	Wild-type N2 Bristol strain	100 μg/ml	Adult stage	–	NA	(Honda et al., 2011)
Royal jelly water soluble faction	*Caenorhabditis elegans*					
	Wild-type N2 Bristol strain	100 μg/ml	Adult stage	–	NA	(Honda et al., 2011)
Royal-jelly protein 30 % Methanol-eluted fraction	*Caenorhabditis elegans*					
	Wild-type N2 Bristol strain	10 μg/ml	Adult stage	–	NA	(Honda et al., 2011)
		10 μg/ml	Adult stage	⇑	NA	
		100 μg/ml	Adult stage	⇑	NA	
		25 μg/ml	Adult stage	⇑	NA	
Royal-jelly protein water-eluted fraction	*Caenorhabditis elegans*					
	Wild-type N2 Bristol strain	10 μg/ml	Adult stage	⇑	NA	(Honda et al., 2011)
		100 μg/ml	Adult stage	⇑	NA	
		25 μg/ml	Adult stage	⇑	NA	
		5 μg/ml	adult stage	⇑	NA	
Royal-jelly proteins	*Caenorhabditis elegans*					
	Wild-type N2 Bristol strain	1 μg/ml	Adult stage	⇑	NA	(Honda et al., 2011)
		10 μg/ml	Adult stage	⇑	NA	
		100 μg/ml	Adult stage	⇑	NA	
Tangerine peel extract	*Drosophila melanogaster*					

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Table 5 (*continued*)

Supplements	Model	Dose	Initiation	Median or mean lifespan	Max. lifespan	Ref.
	W^{1118} strain	0.1 % v/v	3–5 d	⇧	NA	(Oboh et al., 2021)
		1 % v/v	3–5 d	⇧	NA	
VI-28	*Mus musculus*					
	C57BL/6J strain, female	0.05 % w/w	36 wk	⇧	NA	(Ko et al., 2010)
		0.5 % w/w	36 wk	–	NA	
		0.05 % w/w	36 wk	⇧	NA	
		0.5 % w/w	36 wk	⇧	NA	

Abbreviations and symbols: bw: body weight; d: days; m: months; NA: not available; wk.: weeks; ⇧: statistically significant increase; ⇩ statistically significant decrease; –:not significant. Sex only was indicated if both sexes were not included.
VI-28 is a multicomponent herbal formula composed of Radix Ginseng, Cornu Cervi, Cordyceps, Radix Salviae, Semen Allii, Fructus Cnidii, Fructus Evodiae, and Rhizoma Kaempferiae.

(Moriwaki et al., 2013). A dietary supplement containing 31 ingredients increased also mean lifespan in mice (Lemon et al., 2005). A Yang-invigorating Chinese herbal formula starting at 36 weeks of age was able to slightly increase median lifespan in C57BL/6J mice (Ko et al., 2010). However, supplementation with Gcombo, a complex mixture of botanical extracts, vitamins and nutraceuticals, from the age of 12 months had not effect on lifespan of male mice (Spindler et al., 2014). An interesting anti-aging porpoise among compound mixtures is royal jelly produced by the hypopharyngeal, postcerebral, and mandibular glands of the worker honeybees that is the only food consumed throughout their lives by the bee queens which live and reproduce for 1–4 years versus the 3–6-week life of the hive workers (Honda et al., 2011). Royal jelly increased mean lifespan in mice, although the effect of royal jelly on the maximal lifespan of mice was rather disappointing (Inoue et al., 2003). *D. melanogaster* receiving diets containing major royal-jelly proteins (1.25–5.00 %) showed increased mean lifespan and improved both physiological and biochemical measures related to aging flies but also those fed diets containing 1.25 % (w/w) of casein (Xin et al., 2016). Notwithstanding, combinations of various supplements or diets can elicit adverse physiological responses. In that sense, the action of complex preparations including plant extracts is difficult to interpret because, apart from antioxidants, they contain various biologically active products (Le Bourg, 2009; Sadowska-Bartosz and Bartosz, 2014).

In parallel to mean lifespan extension, ferulsinaic acid (Sayed, 2011), EGCG (Abbas and Wink, 2009; Pietsch et al., 2011), sesamin (Yaguchi et al., 2014), quercetin, isorhamnetin and tamarixetin (Surco-Laos et al., 2011) increased resistance against oxidative stress induced by paraquat (Sayed, 2011; Yaguchi et al., 2014) or juglone (Abbas and Wink, 2009; Pietsch et al., 2011; Surco-Laos et al., 2011) in *C. elegans* (Abbas and Wink, 2009; Pietsch et al., 2011; Sayed, 2011; Surco-Laos et al., 2011; Yaguchi et al., 2014). Likewise, dietary administration of blueberry extracts partially restored lifespan and climbing ability after paraquat chronic exposure in wild type *D. melanogaster* (Peng et al., 2012). In case of quercetin, isorhamnetin and tamarixetin, some differences between their effects were found depending on the stage of development of the worm. A significantly greater protection was provided by quercetin than by its methylated derivatives at the 1st day of adulthood, whilst quercetin and isorhamnetin were equally efficient when the oxidative stress was induced in the 6th of day of adulthood (Surco-Laos et al., 2011). In this sense, the expression of oxidation resistance 1 protein was induced by juglone, and this effect was significantly suppressed in *C. elegans*. Likewise, the juglone-induced expression of HSP-16.2 was inhibited by the EGCG treatment. In *C. elegans* exposed to Isorhamnetin, tamarixetin and quercetin, the resistance against thermal stress also resulted significantly increased. However, some differences were found among the assayed compounds, depending on the stage of development of the worm (Surco-Laos et al., 2011). Quercetin offered greater protection when thermal stress was applied in the 1st day of adulthood, whereas tamarixetin was more efficient in worms submitted to stress in the 6th day of adulthood (Surco-Laos et al., 2011). It was also found that black rice extracts at 30 mg/ml could attenuate the paraquat-induced neurodegeneration in wild type flies accompanied by up-regulation of superoxide dismutase (SOD)1, SOD2 and CAT (catalase) in *D. melanogaster* (Zuo et al., 2012).

Although oxidative damage markers were not evaluated in all assays, in general a reduction of those evaluated accompanied to the effect on lifespan by the different antioxidants. Ferulsinaic acid was found to significantly attenuate both lipid peroxidation and the formation of advanced glycation end products in *C. elegans* (Sayed, 2011). Royal jelly reduced DNA oxidative damage in C3H/HeJ mice (Inoue et al., 2003). Nematodes grown on media containing curcumin showed a significantly increased lifespan by reducing the production of ROS (Shen et al., 2013a) and decreased lipofuscin and malondialdehyde levels (Shen et al., 2013a). Chronic melatonin administration between 1 and 10 months of age also rescued the age-dependent mitochondrial oxidative damage in the diaphragm determined by lipid peroxidation levels in female SAMP8 and SAMR1 mice (Rodríguez et al., 2008). Cranberry extract was also associated with a reduced level of 4-hydroxynonenal protein adducts in *D. melanogaster* (Sun et al., 2014). The amount of oxidized protein was significantly lower in worms treated with sorhamnetin, tamarixetin and quercetin (Surco-Laos et al., 2011) or KPG-7 (Moriwaki et al., 2013)-respect than untreated worms. Likewise, intracellular levels of ROS were reduced by EGCG treatment in *C. elegans* (Abbas and Wink, 2009). In addition, curcumin reduced the levels of intracellular ROS in *C. elegans* (Yu et al., 2014) and resveratrol and aloe vera extract in *D. melanogaster* ((Chandrashekara and Shakarad, 2011).

Several studies suggested that antioxidant activity of the tested compound able to expand lifespan would be mediated at least in part as consequence of an indirect action increasing activities of different antioxidant enzymes, which seem to occur by increases in their levels after inducing expression of genes encoding for them. The lifespan extension of *Drosophila* by curcumin supplementation was associated with increased SOD activity (Shen et al., 2013a) and up-regulation of SOD genes expression (Shen et al., 2013a). Polydatin increased SOD-3:: green fluorescent protein (GFP) expression in CF1553 worms (Wen et al., 2014). QRT-PCR results showed that the up-regulation of sod-3 gene expression could also contribute to the increase against stress resistance attributed to EGCG in *C. elegans* (Zhang et al., 2009). Lifespan extension by major royal jelly proteins in *Drosophila* was positively associated with up-regulation Cu- and Zn-SODs (Xin et al., 2016). Up-regulation of genes encoding for SOD1, SOD2 and CAT was increased in black rice extracts-treated *D. melanogaster* (Zuo et al., 2012). The analogous effect of black rice extract is most likely due to upregulating the genes of SOD1, SOD2 and CAT at the transcriptional level (Zuo et al., 2012). In female SAMP8 and senescent resistant (SAMR1) mice, chronic melatonin administration between 1 and 10 months of age rescued GPX and GR activities increasing the GSH:GSSG ratio (Rodríguez et al., 2008). Intensive hydrogen peroxide and paraquat challenge tests showed that lifespan was not extended by blueberry extracts in SOD (n108) or Cat(n1) null mutant strains (Peng et al., 2012). Moreover, lifespan extension induced by cranberry extract in *D. melanogaster* was partially suppressed by knockdown of SOD2 (Sun et al., 2014). Dietary

curcumin at 1.0 mg/g media did not prolongs lifespan of male *D. melanogaster* in presence of the SOD inhibitor, disulfiram (Suckow and Suckow, 2006). Thus, these results suggest that lifespan expansion by curcumin, blueberry and cranberry extracts would be associated with enhanced SOD activity. Indirect antioxidant effects also can be consequence of metal chelator activities as it has been found for cocoa also in the presence of excess heavy metals, enhancing *D. melanogaster* larval survival to the adult stage on copper or iron-supplemented medium (Bahadorani and Hilliker, 2008). Neuroprotective effects of L-carnosine and EGCG also would depend on the activation of hemeoxygenase(HO)-1 and Hsp72(the inducible form of Hsp70), which play an important role in cytoprotection against oxidative stress-induced cell damage. Moreover, the combined action of both compounds resulted in a synergistic increase of HO-1 expression which suggests a crosstalk between the HO-1 and the Hsp72-mediated (Davinelli et al., 2013).

As with dose-response relationship, it was expected that compounds with a higher "antioxidant" activity would exert a higher effect on lifespan, at least within certain range. However, to date, it seems not clear which of the multiple parameters related to redox biology are more suitable to establish which substance is more antioxidant in living organisms. The existence of some studies simultaneously testing the effect of several antioxidants on longevity allows to deepen in this issue. In *C. elegans* under juglone-induced oxidative stress. Thus, Surco-Laos et al. (2011) reported that isorhamnetin and quercetin, but not tamarixetin increased survival at sixth day of adulthood. However, the treatment with any of the three compounds increased *C. elegans* longevity under standard conditions. In contrast, Grünz et al. (2012) reported that naringin that reduced ROS levels in a lower degree than myricetin, quercetin and kaempferol had no statistically significant effect on lifespan, whereas the other compounds extend it. More interestingly, naringin was not able to reduce mitochondrial ROS levels respect to control worms whereas these were reduced by the treatment with the other compounds. Similarly, protein carbonyl content was not reduced by naringenin treatment. The last marker was not affected by kaempferol treatment, which can correlate with the lower effect on mitochondrial ROS levels respect than those observed in worms treated with myricetin and quercetin. This could explain why the statistically significance found for its effect on lifespan was lower compared with the other compounds. On the other hand, Pietsch et al. (2011) who reported a higher in vitro total antioxidant capacity for caffeic acid, followed by rosmarinic acid and then quercetin, found a higher total antioxidant capacity of water-soluble substances extracted from increased in quercetin and caffeic acid-treated worms. The authors suggested that these results could be due to a lower bioavailability of rosmarinic acid. Altogether, these findings suggest that the role of antioxidants increasing cell defenses against mitochondrial ROS production or its ability to targe this organelle could be much relevant for expanding lifespan than its ROS scavenging activity. However, among the studied reviewed here, the effects on lifespan were not compared between treatments with different compounds in those that also assessed parameters related to redox biology.

On the other hand, some results suggest that antioxidant activity do not necessarily contribute to augment longevity. Lipoic acid reduced indices of oxidative stress increasing glutathione levels and decreasing the concentration of lipid peroxidation products and glutathione peroxidase activity. However, this treatment actually decreased the lifespan of SAMP8 mice (Farr et al., 2012). Moreover, in some cases, there is no correlation between the life-prolonging effects and antioxidant properties. Lifespan of *C. elegans* is increased by quercetin, quercetin 3-O-β-D-glucopyranoside, and quercetin 3-O-β-D-glucopyranoside-(4 → 1)-β-D-glucopyranoside, but no direct correlation was found between antioxidative activity and antiaging activity (Xue et al., 2011). Similarly, no correlation was found between the antioxidant activities of cortex *of Magnolia officinalis, Curculigo orchioide, Glycyrrhiza uralensis, Psoralea corylifolia, Cratoxylum cochinchinense* or pine bark and their lifespan benefits in *C. elegans* (Pun et al., 2010). Similarly, in a study comparing the effects of S,S-Trolox-carnosine, R,S-Trolox-carnosine and carnosine on *D. melanogaster*, no correlation between antioxidant protection of rat neurons and the effect on life span of the flies was found (Stvolinsky et al., 2010).

Mitochondrial function also is very important for redox homeostasis since this organelle is considered the main source and target of ROS. The effect on longevity of a chronic melatonin administration between 1 and 10 months of age in female SAMP8 and senescent resistant (SAMR1) mice also rescued the age-related reduction in the mtETC activities and in ATP levels which correlated with prevention of mitochondrial oxidative damage (Rodríguez et al., 2008). Likewise, the level of cellular ATP was lower at 3 days of age in worms treated with KPG-7 than in untreated worms, although mitochondrial function was not measured (Moriwaki et al., 2013). Therefore, although this aspect has been less evaluated, it could be an important target for future research with antioxidants.

4. Antioxidants bioavailability and anti-aging effects

Antioxidant effect on lifespan and age-associated changes could depend on the amount reached in different cell structures and compartments. Thus, the lack of effects observed in some assays might be due to low effective doses. In fact, some exposure levels are difficult to estimate in many assays in invertebrate models since the administered antioxidants may not be fully taken up, especially when added to complex media. In fact, in many studies in *C. elegans*, chemicals are orally delivered by incorporating them into the nematode growth media or mixing with the food bacteria. Importantly, the use of liposomes loaded with water-soluble substances resulted in successful oral delivery of chemicals into the intestines of *C. elegans*. Moreover, oral administration of hydrophilic substances such as ascorbic acid, *N*-acetyl cysteine, GSH, and thioproline using liposomes prolonged the lifespan of the nematodes, whereas the conventional method of delivery showed no longevity effects (Shibamura et al., 2009). Similarly, exposure of *C. elegans* to lactoferrin liposomes led to lifespan extension and reduction of acute oxidative stress, which in addition occurred in a dose-dependent manner. Moreover, immune system stimulation, together with enhancement, cellular adhesion processes and neurogenesis were improved; the immune system was stimulated, and processes involved in the response against oxidative stress were enhanced by the treatment (Martorell et al., 2017). Alternatively, antioxidants delivery can be significantly improved by the use of nanoparticles that differ in chemical composition, size, shape, surface charge and chemistry, and coating and dispersion status conferring antioxidant properties to them. These can efficiently attenuate oxidative stress by penetrating specific tissues or organs, even when administered at low concentrations and it has been found an increase of the lifespan of model organisms in different assays testing them. In this sense, oral administration of tocotrienol, astaxanthin, or γ-tocopherol to *C. elegans* prolonged its lifespan, but only when the compounds were delivered by γ-cyclodextrin micro-particles of inclusion (Kashima et al., 2012). In another study, sesamin/γ-cyclodextrin inclusion compounds administrated to *C. elegans* young adulthood also increased mean lifespan and contributed to locomotion maintenance. However, the accumulation of protein carbonyls and lipofuscin was similar in sesamin-exposed and control worms, suggesting that sesamin is unlikely to work simply as an antioxidant (Yaguchi et al., 2014). Therefore, it seems that differences between studies about longevity-promoting effects of the antioxidant could be a consequence of its bioavailability, but the relevance of its described antioxidant activities is not clear, at least in all cases. Despite the use of nanotechnology offers an interesting field to continue investigating on life-expanding substances, it is important to note concerns about toxicity of the nanoparticles.

5. Factors conditioning the lifespan expanding effect of antioxidants

Although some antioxidants have shown an antiaging effect in wild-type models under "normal" or standard conditions, there are many studies evaluating their effects in models with certain genotypes or under some conditions that have consequences in their lifespan or age-associated changes. In invertebrates, some antioxidants had life-prolonging effects on mutants deficients in antioxidant defenses or animals subjected to oxidative stress with better results compared to those observed in wild-type individuals or under standard conditions. For instance, in *C. elegans* under acute stress conditions, polydatin treatment increased mean lifespan by up to 62 % compared with the 31 % observed under normal conditions (Wen et al., 2014). Similarly, ascorbic acid partially rescued the lifespan of SOD-deficient yeasts which has been considerably reduced as a result of lack of this vital antioxidant enzyme (Krzepiłko et al., 2004). Likewise, mitochondria-targeted CoQ mitoquinone (MitoQ) rescued pathology associated with compromised defenses observed in SOD-deficient flies, but failed to extend the lifespan of normal, wild type, animals (Magwere et al., 2006). In this sense, EGCG (Abbas and Wink, 2009) and CoQ_{10} (Ishii et al., 2004) were also able to recover the decreased lifespan in *C. elegans* mev-1 null mutants that are hypersensitive to age and oxidative stress, probably because of elevated superoxide anion production in mitochondria since mev-1 gene encodes cytochrome *b*, a large subunit of the Complex II enzyme succinate-CoQ oxidoreductase. Additionally, CoQ_{10} also suppressed supernumerary apoptosis (Ishii et al., 2004), another phenotype feature of the model. In another assay, EGCG treatment was able to increase mean lifespan of *C. elegans* under oxidative stress conditions but not under normal conditions (Zhang et al., 2009) However, other antioxidant including alpha-tocopherol (Ishii et al., 2004), catechin (Saul et al., 2009) and curcumin (Liao et al., 2011; Yu et al., 2014) failed to prolong lifespan in mev-1 null *C. elegans* mutants. A possible reason of the lack of effect of some antioxidants the mentioned assays could be that the used dosage was not enough to counteract excessive ROS production. In this sense, it was reported that the amount of EGCG needed to expand life in mev-1 null mutant was higher than those required in wild-type individuals (Pietsch et al., 2011).

However, the improved effects mentioned above were not found for other antioxidant under other pro-oxidant conditions. Under hyperoxia or in a Cu/Zn-SOD-deficient background, cocoa extract also exhibited a strong antioxidant activity, increasing the average lifespan of *D. melanogaster* (Bahadorani and Hilliker, 2008). Nevertheless, cocoa supplementation in a Mn-SOD-deficient background enhanced an earlier mortality accompanied by a loss of climbing ability. Moreover, the treatment with the same extract at higher concentration increased survival under both conditions, despite it had no effect in wild-type individuals under standard conditions. This suggested that cocoa extract may act as a mitochondrial oxidant under conditions of extreme oxidative stress, which also depend on its concentration (Bahadorani and Hilliker, 2008). In another assay in honeybees, it was found that lifespan extension effects of resveratrol were abolished under hyperoxic stress (Rascón et al., 2012). In this sense, long-term supplementation of mice with Rikkunshito, a Japanese traditional herbal medicine that induces NPY activation, upregulated anti-oxidative gene expression in liver under oxidative stress induced by 3-nitropropionic acid or doxorubicin, although it did not affect the survival rate (Wang et al., 2020). Therefore, antioxidants can be beneficial only at certain dose and this seemed to depend on redox state of the cells.

In this sense, many antioxidants have been assessed in rodent models fed on "unhealthy" diets such as high-fat diets, cholesterol and fat-rich diets or diets rich in fat and sugar. Moreover, in individuals with overweight or obese, resveratrol usually displays antiaging effects and metabolic regulation (Marchal et al., 2013). Resveratrol extends life in diverse model organisms when administered late in life (Ghosh et al., 2013; Lee et al., 2016; Orlandi et al., 2017). However, in normal diet-fed mice, resveratrol did not increase lifespan, despite doing so for high-fat diet-fed mice (Bhullar and Hubbard, 2015; Novelle et al., 2015). A polyphenol-rich plant extract was able to increase median lifespan in mice with hyperglycaemia and hypercholesterolaemia induced by a high-fat/high-sucrose diet, although without effect on diet-induced obesity of adiposity (Aires et al., 2019). Survival time was increased C57BL/6J mice from 14-weeks-of-age maintained in a high fat diet, but also supplemented with grapes that are rich in proanthocyanins. Moreover, oxidative damage at liver was prevented and nonalcoholic fatty liver disease was ameliorated hepatic gene expression was modulated with enhancement enhanced Gstp1 Gpx4 and 8, Gss, Gpx7, Sod1 expression by dietary grape supplementation. In addition, 14 genes responsible for the metabolism, transportation, hydrolysis, and sequestration of fatty acids were upregulated whereas genes responsible for lipid content and cholesterol synthesis were downregulated (Dave et al., 2022).

Again, despite CoQ_{10} supplementation was ineffective for increasing lifespan in most of the studies in both rats and mice (Lee et al., 2004; Lönnrot et al., 1995; Sohal et al., 2006), CoQ_{10} supplementation would be effective in increasing median life span when it was combined with certain nutritional conditions associated with elevated oxidative stress. In a study on rats comparing isocaloric diets enriched on different lipid profiles by using virgin olive, sunflower or fish oils as a dietary fat source, supplementation with a low dose of CoQ_{10} from weaning was able to improve survival in rats receiving a diet with sunflower oil as fat source, increasing median lifespan values. However, no effects were observed in those fed on diets based on virgin olive or fish oil (Ramirez-Tortosa et al., 2020). These effects were also observed when sunflower oil was administered in a proportion of 8 % w/w in the diet, which is the double of current recommendations for rodents (Quiles et al., 2004). In parallel, an aging-associated increase in urinary F2-isoprostanes was prevented by the addition of CoQ_{10} to the diet, which suggests that CoQ_{10} benefits could be a consequence of a reduction in oxidative stress promoted by sunflower oil (Varela-López et al., 2017b). In gums, an age-related increase in the expression of genes involved in mitochondrial biogenesis and antioxidant defense were also found (Varela-Lopez et al., 2016). Such changes could also occur in other tissues, contributing to reducing oxidative stress. However, many of these effects were present only when animals were fed on diets using sunflower oil as a unique dietary fat source. The protective effects of CoQ_{10} have also been observed when this molecule was added to similar diets but with a high-fat content (8 % w/w) (Huertas et al., 1999; Ochoa et al., 2007, 2005, 2011; Quiles et al., 2005, 2004, 2010). In contrast, the effects of CoQ_{10} on animals receiving diets with low-oxidizable edible oils as unique fat source were not so clear (González-Alonso et al., 2015; Varela-Lopez et al., 2016; Varela-López et al., 2017a). The lack of effect exerted by CoQ_{10} was accentuated when it was added to a diet using virgin olive oil since there were practically no changes in markers related to aging in different tissues and organs or improvements in health (Varela-Lopez et al., 2016; Varela-López et al., 2017b). These results support that idea that antioxidants improve longevity under "unfavorable" circumstances since the results of studies comparing the effects of different unsaturated fat on aging or certain age-related diseases suggest that polyunsaturated fatty acids (PUFA) would be detrimental for health which correlated with oxidative stress (Ochoa et al., 2003; Quiles et al., 2002). In fact, the degree of unsaturation of lipid of cell membranes has been proposed to be an adaptation of cellular membranes to oxidative stress (Naudí et al., 2013) contributing to explain differences in longevity between species (Pamplona et al., 2002, 2013; Pamplona and Barja, 2003).

Thus, it seems that antioxidants could be useful to counteract the consequences of unhealthy diets that "accelerate" the aging process, but they have no additional effects under more favorable conditions. Considering the reported positive effects of some antioxidants in invertebrate models, it is also interesting to consider that certain animal models used in the laboratory and considered wild-type animals can be particularly susceptible to oxidative stress as consequence of genetic

drift, founder effects and even some selective pressures derived from the laboratory conditions. This would explain why dietary antioxidants also have longevity-promoting effects under "normal" conditions or in individuals with "wild-type" phenotypes. In support of that idea, it was reported that dietary supplementation with either vitamin E or ascorbic acid on a wild-derived animal, short-tailed field vole (*Microtus agrestis*) for nine months shortened lifespan in voles maintained under both cold and warm conditions (Selman et al., 2013).

6. Non-antioxidative activity of antioxidants

In many assays with antioxidants, only markers related with redox biology have been assessed together with lifespan or functional parameters. However, there is increasing evidence for additional activities able to counteract age-related associated changes and mechanisms leading them, which could be important contributors to their anti-aging effects, explaining differences found between experiments and tested molecules. In this sense, some antioxidants have shown to induce autophagy in certain models, an effect also described for other longevity-promoting interventions, including dietary restriction and inhibition of TOR with rapamycin. Seemingly, clearing cellular damage by autophagy is a common denominator of many lifespan-extending manipulations (Sadowska-Bartosz and Bartosz, 2014). Resveratrol or the natural polyamine spermidine, have often been associated with autophagy and in some cases, it was reported to require autophagy for their effects. Other antioxidants has been described to act as senolytics, selectively targeting and removing senescent cells. This has been reported for quercetin that combined with dasatinib effectively clears senescent cells and senescence-associated secretory phenotypes in vitro and in aged humans and mice (Krzystyniak et al., 2022; Lin et al., 2021; Zhou et al., 2021a, 2021b). Lastly, certain age-related changes in the immune system, or immunosenescence, have been also postulated as responsible for aging, which is supported by the reported age-related functional decline in the immune system, an increasing level of autoimmune phenomena, and the involution of the thymus gland (Lipsky and King, 2015). In fact, aging is associated with a pro-inflammatory state and inflammation is involved in etiopathology of multiple conditions, many of them considered as age-related diseases. Moreover, there is a bidirectional relationship between oxidative stress and inflammation. Some antioxidants also reduce markers of inflammation. In this sense, tetrahydrocurcumin has been associated with the recovery from renal injury in mice and in anti-inflammatory responses (Kitani et al., 2007). Likewise, EGCG decreased the mRNA and protein expressions of nuclear factor κB (NF-κB), a key proinflammatory transcription factor, in treated mice (Niu et al., 2013).

7. Cell signaling pathways modulation by antioxidants

According to programmed theories, an internal biological clock regulates development, growth, maturity, and aging by sequentially switching genes on and off (Lipsky and King, 2015; Rodríguez-Rodero et al., 2011). Recent advances in aging research have uncovered genes and genetic pathways that influence lifespan in such diverse organisms as yeast, nematodes, flies, and mice. However, no single identified gene completely controls aging, consistent with the concept that the genetic control of aging is multifactorial. It has been postulated "aging genes" that would exert their effects by slowing or stopping biochemical metabolic pathways (Lipsky and King, 2015; Park and Yeo, 2013). Changes in gene expression and biochemical metabolic pathways could be the results in the modulation of nutrient-sensing pathways, which detect and respond to nutrient levels and initiate downstream cascade responses such as growth, energy, and reproduction. Suppression or mutations of components of these pathways expand lifespan in diverse model organisms (Blüher et al., 2003; Kenyon, 2010). The most widely studied nutrient-sensing signaling pathways in relation to aging biology are sirtuins/NAD^+, AMP-activated protein kinase (AMPK), targets of rapamycin (TOR), and insulin/Insulin-like growth factor (IGF)-1 pathways, although most of the mechanisms according to which these pathways control aging remain unclear.

Sirtuins are primarily mammalian protein deacetylases that utilize nicotinamide adenine NAD^+ as a coenzyme to pull out acyl groups from numerous proteins. Its importance in aging seems clear since overexpression of some specific sirtuins or their orthologues increases lifespan in yeast, worms, flies, and humans (Imai and Guarente, 2014; Wątroba et al., 2017). SIRT1 is the most widely and extensively studied sirtuin in aging research. Main effects are derived from deacetylation and stimulation of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1α), culminating in the modulation of mitochondrial biogenesis, cell cycle, apoptosis, autophagy, lipid metabolism, and endothelium-dependent vasodilation (Bonkowski and Sinclair, 2016; Imai and Guarente, 2014) (Table 6). Resveratrol is able to increase the deacetylase activity of human sirtuin 1 (SIRT1) (Howitz et al., 2003). Long-term dietary resveratrol activated AMPK pathways and SIRT1 in SAMP8 and SAMR1 mice (Porquet et al., 2013). EGCG increased the upstream protein expressions of silent mating type information regulation of SIRT1 homologue in mice (Niu et al., 2013). In addition, part of the observed effects can be also consequence of changes in cell NAD^+/

Table 6
Downstream effect of nutrient-sensing signaling pathways and its role in lifespan extension by supplements.

Nutrient-sensing signaling pathways	Downstream effects	Compounds in which lifespan extension effect could be involved
Sirtuins/NAD	PGC-1α activation: • Mitochondrial biogenesis • Cell cycle progression • Apoptosis inhibition • Autophagy induction • Lipid metabolism stimulation • Endothelium-dependent vasodilation	• Resveratrol • EGCG • Apple procyanidins • Curcumin
AMPK	TOR complex inhibition: • Autophagy induction • Lipid biosynthesis inhibition • Protein synthesis inhibition PGC-1α activation: • Mitochondrial biogenesis Acetyl coenzyme A carboxylase inhibition: • Lipid biosynthesis inhibition • Lipid oxidation stimulation	• Resveratrol (sirtuin-dependent) • EGCG • Oxaloacetate
Insulin/IGF-1 signaling pathway	Induction of FOXO genes • Induction of antioxidant enzymes • Others	• Astaxanthin • Sesamin • Oxaloacetate • Myricetin • Quercetin • kaempferol • Naringenin • Catechin • Ferulic acid • Curcumin • Cranberry extract • Black rice extracts • Blueberry extracts

AMPK: AMP-activated protein kinase; EGCG: epigallocatechin gallate; IGF Insulin-like growth factor; PGC-1α: peroxisome proliferator-activated receptor γ co-activator 1 α; FOXO: Forkhead box O; TOR: target of rapamycin.

NADH ratio that has a broad impact on cellular physiological processes and these changes may depend also on other situins. In this sense, resveratrol has shown to require increased sirtuin 2 (SIR-2) activity in diverse model organisms including yeast, *C. elegans*, and *D. melanogaster* to extend lifespan (Ghosh et al., 2013; Lee et al., 2016; Orlandi et al., 2017). Likewise, *C. elegans* lifespan extension by apple procyanidins (Sunagawa et al., 2011) and curcumin (Shen et al., 2013a; Yu et al., 2014) has been also reported to occur in a SIR-2-dependent manner. Similarly, oxidative stress response inhibition by tetrahydrocurcumin in *D. melanogaster* was associated with Sir2 regulation (Shen et al., 2013a). In case of resveratrol, the activation of SIRT1 seems to be mediated by binding to the molecule, but its activity is weak (Cao et al., 2015).

AMPK is a serine/threonine kinase stimulated by energy stress (low ATP:ADP ratio) and two upstream regulators: liver kinase B1 and calcium/calmodulin-dependent protein kinase. (Carling, 2017; Oduro et al., 2020). Activated AMPK directs metabolism towards catabolism through varied stimulation of multiple pathways, including mTOR complex 1 signaling and internal homeostasis processes, such as lipid and mitochondrial homeostasis, through acetyl coenzyme A carboxylase and PGC-1α, respectively (Table 6). There is a profound role of AMPK in cellular metabolism, contributing also to the maintenance of intracellular quality control processes. The increase in lifespan observed in oxaloacetate-supplemented *C. elegans* was also dependent on AMPK (Williams et al., 2009). EGCG has shown to trigger AMPK activity in laboratory disease, but this could be the result of SIRT1 activation (Yuan et al., 2020). Importantly, AMPK activation seemed to require upstream activation of SIRT1. In fact, resveratrol could not activate AMPK in the absence of SIRT1 (Price et al., 2012) and similarly, AMPK-dependent improvements in mitochondrial function and biogenesis were not observed in SIRT1 negated mice.

mTOR complex 1 activation stimulates anabolic processes, lipid biosynthesis, and protein synthesis. These effects are conducted via mTOR complex 1-mediated phosphorylation of its downstream substrates ribosomal protein S6 kinase one and eukaryotic translation initiation factor 4E binding protein 1. Moreover, mTOR complex activation suppresses lipolysis and autophagy (the degradative signals often likened to cellular homeostasis maintenance) (Johnson et al., 2013; Saxton and Sabatini, 2017) (Table 6). Also, the fact that EGCG induces autophagy further implies its ability to affect an mTOR-centered network to improve metabolic health and longevity (Brimson et al., 2021).

The importance of Insulin/IGF-1 signaling pathway for lifespan extension by different molecules considered antioxidant have been widely evidenced in invertebrates. Forkhead box O (FOXO) genes represent a subfamily of conserved transcription factors that act as key regulators of longevity downstream of insulin and insulin-like growth factor signaling in mammals (Table 6). DAF-16 is the closest *C. elegans* homologue of FOXO. Experiments in daf-16 null mutant *C. elegans* have indicated that DAF-16 is required for lifespan extension by astaxanthin (Yazaki et al., 2011), sesamin (Yaguchi et al., 2014) and oxaloacetate (Williams et al., 2009) as well as for reduction of ROS levels in *C. elegans* by EGCG (Brown et al., 2006). Moreover, it was proved that DAF-16 protein was translocated to the nucleus in the astaxanthin-exposed wild type *C. elegans* (Yazaki et al., 2011). Lifespan increase in *C. elegans* by myricetin, quercetin, kaempferol, or naringenin involved an enhancement in DAF-16 translocation (Grünz et al., 2012). qRT-PCR results showed that the up-regulation of daf-16 could also contribute to the stress resistance attributed to EGCG in *C. elegans* (Zhang et al., 2009). Other components of insulin-like signaling also have been reported to be necessary for pro-longevity effects of antioxidants. Experiments in daf-2 (the insulin receptor homologue) null mutants provided results in the same sense for sesamin (Yaguchi et al., 2014) catechin (Saul et al., 2009), and ferulic acid (Li et al., 2021). Lifespan extension by cranberry extract in *D. melanogaster* was associated with slightly increased phosphorylation of AKT (Sun et al., 2014), that is involved in DAF-16 activation. On other hand, lifespan extending phenotype after catechin treatment was absent in *akt-2* null mutants (Saul et al., 2009). This was also reported for the found effect of curcumin on survival in *C. elegans akt-1* null mutants (Yu et al., 2014). In addition, treatments with black rice (Peng et al., 2012) and blueberry (Zuo et al., 2012) extracts led to the down-regulation of Methuselah (*Mth*) in assays showing an increase of mean lifespan in *D. melanogaster*. It has been reported that reduced *Mth* signaling also inhibits insulin secretion from the in insulin-producing cells of the fly brain, and therefore, the longevity enhancement might come from the reduced insulin/IGF-1 like signaling (Gimenez et al., 2013). Additionally, the effects on DAF-16 would be responsible for their indirect antioxidant activity since DAF-16 translocation to the nucleus would induce the expression of genes encoding for antioxidant enzymes. In *C. elegans*, DAF-16 has been reported to induce the expression of *sod2* gene and it would be related to an increase of *sod-3* promoter activity in *C. elegans* treated with myricetin, quercetin, kaempferol or naringenin (Grünz et al., 2012) and with an increased expression of genes encoding for CAT and SOD genes in *C. elegans* treated with astaxanthin (Yazaki et al., 2011). An up-regulated expression of genes encoding for SOD, CAT, and Rpn11 subunit of the proteasome lid subcomplex was reported to occur in *D. melanogaster* treated with extracts of black rice (Peng et al., 2012) or blueberry (Zuo et al., 2012). Similarly, curcumin also up-regulated expression of SOD genes in *D. melanogaster* (Shen et al., 2013a). qRT-PCR results showed up-regulated expression of *sod-3* in EGCG treated *C. elegans* (Zhang et al., 2009). Interestingly, EGCG at 200 μM but not 1000 μM of EGCG extend life in *C. elegans* due to nuclear accumulation of DAF-16 which accelerated the biological aging process. Nonetheless, combining high-dose EGCG with theanine reversed high-dose EGCG lifespan reduction in *C. elegans* (Peng et al., 2021). Therefore, this pathway could be also involved in deleterious effects on health.

Therefore, it seemed that the effect of many compounds considered antioxidant could depend on the modulation of multiple cellular processes beyond antioxidant defense systems. However, it is not clear how these compounds are able to modulate various of the mentioned pathways. Importantly, dietary antioxidants, such as polyphenols, have been demonstrated to be protective through the activation of hormetic pathways, including genes controlling cell stress response and proteasomal activity degrading oxidatively modified proteins (Calabrese et al., 2012; Rattan, 2012). A hormetic action of quercetin and other flavonoids on *C. elegans* has been documented (Kampkötter et al., 2007). Paradoxically, the effect of hormesis may be mediated by increased formation of ROS since they can act as essential signaling molecules to promote metabolic health and longevity (Ristow and Schmeisser, 2011). As mitochondria is believed to be the cell main source of ROS, it seems that promotion of ROS specifically by mitochondria evokes an adaptive response that culminates in subsequently increased stress resistance assumed to ultimately cause a long-term reduction of oxidative stress. Due to the relevant role that mitochondria play in this phenomenon, it is known as mitochondrial hormesis or mitohormesis.

Expression of genes encoding for antioxidant enzymes also depend on nuclear respiratory factor (Nrf) proteins that are members of the CNC (cap 'n' collar) family of transcription factors that are master regulators of oxidative stress resistance and longevity (An and Blackwell, 2003; Blackwell et al., 2015; Kahn et al., 2008; Sykiotis and Bohmann, 2008). These are known to be activated by high ROS levels. Protein skinhead-1 (SKN-1) is the single functional CNC homologue found in *C. elegans*. Curcumin (Yu et al., 2014), ferulic acid (Li et al., 2021) and sesamin (Yaguchi et al., 2014) effects in *C. elegans* has been reported to be skn-1-dependent. Similarly, qRT-PCR results suggested the up-regulation of skn-1 in *C. elegans* treated with EGCG (Zhang et al., 2009). The expression of the gst-4 and hsp-16.2 stress response genes, their downstream genes, have been reduced by curcumin treatment in *C. elegans* which correlated with effects on intracellular ROS (Yu et al., 2014). The increase in all these proteins could be consequence of transient increases in ROS levels.

Moreover, recent observations suggest that catechins can exert

prooxidant activity, particularly at high concentrations. Catechins, particularly EGCG at 100 μM, have also been shown to increase oxidative damage incurred after exposure of DNA to 8-oxo7,8-dihydro-2-deoxyguanosine (Furukawa et al., 2003). A hormetic mechanism of action has been reported for the effects of *Ginkgo biloba* extract on the lifespan of *C. elegans* (Wu et al., 2002). In case of complex extracts, it has been suggested that they can also contain toxins produced by plants against insects and microorganisms, which may induce a hormetic effect (Le Bourg, 2009). However, it is not clear what is the relevance of hormesis for delaying aging in mammals, but there are reasons to assume that it modulates universal mechanisms of aging and delay aging of mammals even if these effects are not of a large magnitude (Le Bourg, 2009). Like toxins, they act in some concentration range, their high concentrations being usually toxic.

8. Conclusions

According to oxidative damage theory of aging, antioxidants should slow down aging and prolong lifespan and healthspan. An enormous number of studies aimed at finding a relationship between addition of exogenous antioxidants on the course of aging and lifespan of model organisms. Many of them have shown to increase mean lifespans in aging models, especially in invertebrate models, but the number of studies showing maximum lifespan extension by treatment with antioxidants is very reduced. In addition, despite some studies reported life extending effect for certain antioxidants, others did not support it for the same compound. Importantly, some treatments have reduced lifespan. Possible reasons explaining all these differences can lay in the therapeutical window of each compound as well as its bioavailability. Moreover, under "unhealthy" conditions they seem to improve health in mots cases, but this depended on the evaluated antioxidant. This is particularly interesting for animals maintained on "unhealthy" diets. Therefore, supplementation with antioxidants could result useful to improve healthspan but to ascertain if it is possible to increase maximum longevity with this type of intervention requires more research. Antioxidant activity seems to be mainly based on indirect mechanisms since antioxidant enzymes use to be increased by the treatments in most of cases. Since many of antioxidative mechanisms exerted by these compounds are due to indirect mechanisms, it seems that changes at the gene expression level by modulation of nutrient-sensing and other additional pathways seems to be crucial. Concerning that, hormesis, probably due to transiently enhancing mitochondrial ROS levels, is an interesting phenomenon to explain the effects observed in certain assays. On the other hand, treatments with antioxidant molecules or mixtures could lead to a reduction of endogenous antioxidants or to an excessive oxidative stress under certain circumstances with deleterious consequences for animal longevity. For this reason, it is already needed to clarify all the biological activities that compounds considered antioxidant could exert in the cells as well as possible differences in these activities according to dosage, bioavailability, age, sex, nutritional context or even physical activity of individuals reviving the treatments.

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