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Scientific evidence of foods that improve the lifespan and healthspan of different organisms

So-Hyun Park[1], Da-Hye Lee[3], Dae-Hee Lee[4] and Chang Hwa Jung[1,2]*

[1]*Aging and Metabolism Research Group, Korea Food Research Institute, Wanju-gun, Jeollabuk-do, South Korea*
[2]*Department of Food Biotechnology, University of Science and Technology, Wanju-gun, Jeollabuk-do, South Korea*
[3]*Department of Biochemistry, Molecular Biology, and Biophysics, University of Minnesota, Minneapolis, MN, USA*
[4]*Department of Marine Food Science and Technology, Gangneung-Wonju National University, Gangneung, Gangwon-do, South Korea*

Abstract

Age is a risk factor for numerous diseases. Although the development of modern medicine has greatly extended the human lifespan, the duration of relatively healthy old age, or 'healthspan', has not increased. Targeting the detrimental processes that can occur before the onset of age-related diseases can greatly improve health and lifespan. Healthspan is significantly affected by what, when and how much one eats. Dietary restriction, including calorie restriction, fasting or fasting-mimicking diets, to extend both lifespan and healthspan has recently attracted much attention. However, direct scientific evidence that consuming specific foods extends the lifespan and healthspan seems lacking. Here, we synthesized the results of recent studies on the lifespan and healthspan extension properties of foods and their phytochemicals in various organisms to confirm how far the scientific research on the effect of food on the lifespan has reached.

Key words: **Aging: Lifespan extension: Healthspan: Phytochemicals**

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Introduction

Advances in medical technology have increased the human lifespan. However, because the elderly often suffer from long-term illness before death, research on healthspan (i.e. disease-free period) and the development of strategies to promote healthy ageing are needed to reduce the economic burden and improve quality of life, representing a shift from research focused only on increasing the lifespan. During the ageing process, the structure and physiological functions of the body gradually deteriorate and the mortality rate increases over time, regardless of disease status. Therefore, ageing is a complex physiological phenomenon, and strategies to reduce the effects of ageing require contributions from various fields. Recently, epigenetic alterations, genomic instability, telomere attrition, loss of proteostasis, dysregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication have been proposed as major molecular biological causes of ageing. Factors involved in the overall ageing phenomenon are closely connected, rather than being responsible for a single aspect of the process[1,2].

Healthspan is significantly affected by the quality and amount of food as well as the timing of the meals. Studies have shown that ageing can be controlled via several dietary approaches such as caloric restriction, time-restricted eating, intermittent fasting, and low-carbohydrate and ketogenic diets[3]. In addition, from the viewpoint of functional foods, specific food extracts and their components (i.e. phytochemicals) can prevent chronic and age-associated diseases related to reactive oxygen species (ROS). Diets with anti-ageing abilities have been proposed, especially ones based on polyphenol-rich foods[4].

Nevertheless, studies on the molecular mechanisms by which consuming specific foods contributes to the lifespan and healthspan have not received much attention. Most studies of the effects of certain foods on ageing have been conducted from the perspective of disease prevention and treatment in cellular and rodent models, in addition to cohort studies of the benefits of a vegetarian diet. However, studies of beneficial foods from the viewpoint of biological ageing are rare. Recently, a paradigm shift to the view that ageing is not an unavoidable natural phenomenon but can be actively controlled has prompted a transition from research focused on improving degenerative diseases to studies focused on the biological control of ageing at the pre-disease stage[5–7]. Therefore, studies of ageing control mechanisms and the prevention of ageing-related diseases to achieve healthy ageing through a diet of specific foods are needed.

Studies of lifespan and healthspan are mainly based on *Caenorhabditis elegans* and *Drosophila melanogaster* models, which benefit from short life cycles. Several studies have evaluated the mechanisms by which specific foods promote

* **Corresponding author:** Chang Hwa Jung, email: chjung@kfri.re.kr

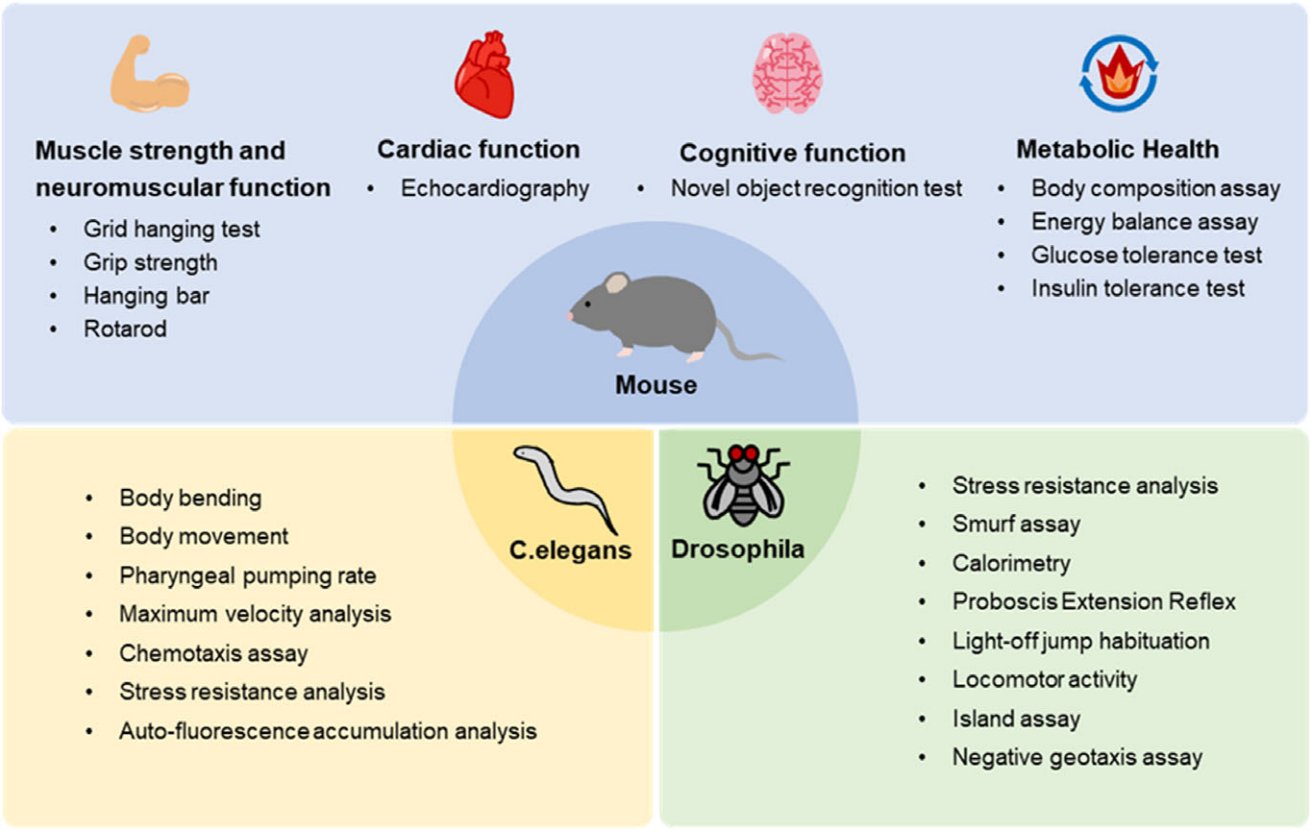

Fig. 1. Evaluation of healthspan in aged mouse, *C. elegans* and *Drosophila*.

lifespan extension and healthy ageing in these models. Furthermore, methods for the evaluation of healthspan in primates are being established and utilized[8]. Here, we review trends in research on lifespan extension via diets of specific foods or their components over the past 20 years in different organisms. In particular, this review focuses on ongoing food research from a healthspan perspective.

Lifespan and healthspan

Whereas lifespan is a quantitative index, healthspan is an index that reflects qualitative aspects of health potentially compromised by diseases related to metabolism, learning and cognition, cardiovascular and sarcopenia. The global lifespan is 73·2 years, compared with an estimated healthspan of 64 years. This gap indicates that further improvements in quality of life are needed[9]. The elderly population is expected to double over the next 30 years. Because a longer life is associated with more time with chronic diseases, such as Alzheimer's disease, cardiovascular disease and diabetes, there is a need for standardized techniques to assess healthy ageing in preclinical studies. There is growing interest in geroprotective interventions that delay or prevent the onset of these diseases. Recently, Bellantuono *et al.* prepared a 'toolbox' for evaluating health function in mice[8]. This toolbox measures cardiac, cognitive, neuromuscular and metabolic health components. Major ageing research centres in Europe and the United States have adopted this as a standardized tool to analyse the healthspan of mice. Therefore, the use of this toolbox in evaluating healthy ageing with respect to diet is well accepted (Fig. 1).

Foods that prolong lifespan in diverse organisms

In the early stages of research on the effects of food extracts and its components on lifespan, studies were mainly conducted in *C. elegans* and *D. melanogaster*, which have a shorter lifespan than that of mice. In experiments using these organisms, efficacy evaluations and mechanistic studies have mainly used samples extracted with solvents, such as water and ethanol, rather than whole foods. Therefore, it is necessary to differentiate the effects of extracts from those of whole foods. Using the search terms 'food (or phytochemical) & longevity (or healthspan, lifespan)' in PubMed, Google Scholar and Web of Science, we identified more than 400 papers related to lifespan extension and healthspan by foods or phytochemicals published from 2003 to date. In the early 2000s, research on the relationship between lifespan and food was lacking. However, the number of relevant papers has gradually increased since 2010 (Fig. 2a). Among the research models used to evaluate lifespan extension, worms and flies accounted for more than 90% of studies. In particular, studies of worms, which have a short lifespan, were the most common. Experiments using mice have been reported at a constant ratio; however, since a long survival period of more

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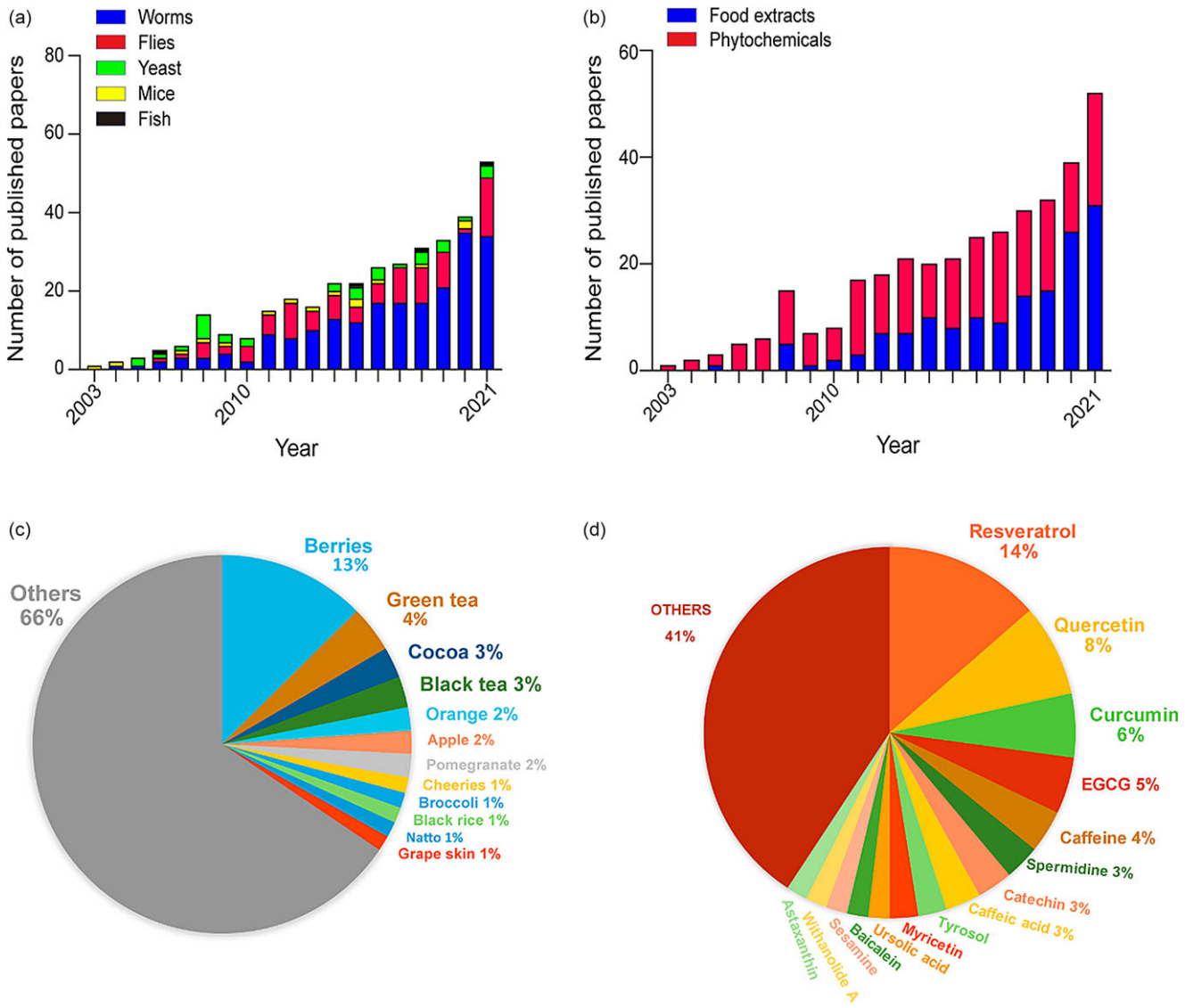

Fig. 2. Analysis of trends in research on the relationship between food and lifespan. (a) Studies based on the effect of diet on lifespan, conducted in different organisms. (b) Study trends based on the effect of food extracts and phytochemicals on lifespan. (c) Frequent food extracts and (d) phytochemicals for which lifespan studies have been performed.

than 24 months is required, their use in actual lifespan studies is greatly limited. In addition, the abundance of studies of life extension by food extracts as well as single compounds has steadily increased (Fig. 2b). However, since most papers are limited to *C. elegans* and *D. melanogaster*, there is insufficient evidence for effects on lifespan in mice or primates.

With respect to food types related to lifespan, berries were the most frequently studied, accounting for 13% of studies, followed by green tea, cocoa, black tea, orange and apple (Fig. 2c). Also, there is evidence for the beneficial effects of extracts from berries, including blueberry, cranberry, mulberry and raspberry, in extending the lifespan of *C. elegans* and *D. melanogaster*. In addition to these species, green tea extract has also been evaluated in mice. With respect to single compounds, resveratrol accounted for 14% of studies related to lifespan, followed by quercetin (8%), curcumin (6%), epigallocatechin-3-gallate (EGCG) (5%), caffeine (4%) and spermidine (3%) (Fig. 2d). Resveratrol is the only drug evaluated with respect to lifespan extension in various models, such as yeast, *C. elegans*, *D. melanogaster* and mice. The extension of lifespan by quercetin has been demonstrated mainly in *C. elegans*, and the effects of curcumin have been demonstrated in flies. EGCG has mainly been studied in mice and rats. The focus on these foods and phytochemicals in studies of life extension can be explained by their well-established beneficial health effects. In addition to these compounds, many other compounds in food have the potential to extend the lifespan and healthspan. Therefore, studies of the efficacy of a larger array of compounds based on scientific evidence are needed.

Foods with beneficial effects on lifespan and healthspan

To confirm how far the scientific lifespan research on food has reached, we investigated the results of recent studies on the

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Table 1. Foods that promote lifespan and healthspan

Extracts	Models	Major molecular mechanism	Lifespan	Healthspan	References
Berries	*C. elegans*	CaMKII signalling and antioxidant activity	↑	↑	(10)
	D. melanogaster	Up-regulation of *sod*, *cat* and *rpn11* and down-regulation of *mth*	↑		(11)
	C. elegans	*hsf-1* activation in transgenic *C. elegans* constitutively expressing Aβ	↑		(12)
	D. melanogaster	Promote longevity at all stages of life	↑		(14)
	D. melanogaster	Modulation of *sod1*, *mth*, *inR*, *tor* and *pepck* genes	↑		(13)
	D. melanogaster	Reduced oxidative stress	↑		(15)
	C. elegans	SKN-1/Nrf-2 pathway	↑	↑	(18)
	C. elegans	DAF-16 translocation into the nucleus	↑		(19)
Green tea	*D. melanogaster*	Increased SOD and CAT activity	↑		(20)
	D. melanogaster	Inhibited reproduction by limiting iron uptake	↑		(21)
	D. melanogaster	Up-regulation of *sod* and *cat*	↑		(22)
	Mice	Increased mid-life survival in female UM-HET3 mice	↑		(23)
Cocoa	*D. melanogaster*	Antioxidant and metal chelating effects	↑		(25)
	Mice	Improved cognitive performances	↑	↑	(26)
Black tea	*D. melanogaster*	Up-regulation of *sod1* and *cat* genes under various oxidative stress	↑		(27)
	C. elegans	Up-regulation of *gsh-px* and *sod-3*			(28)
Orange	*C. elegans*	Up-regulation of *daf*-16, *sod-3*, *gst-4*, *sek-1* and *skn-1*	↑	↑	(29)
	D. melanogaster	DNA protection against free radicals	↑		(30)
	D. melanogaster	Improved locomotor performance, memory index and antioxidant status	↑	↑	(31)
Apple	*D. melanogaster*	Up-regulation of *sod1*, *sod2*, *rpn11* and *cat* and down-regulation of *mth*	↑		(32)
	C. elegans	Improved motility and reduced lipofuscin accumulation	↑	↑	(33)
	C. elegans	Regulation of the insulin signalling pathway and DAF-16	↑	↑	(34)
Pomegranate	*C. elegans*	Extended lifespan in the concentration range of 2·5–5 mg/mL	↑		(35)
	C. elegans	Activation of *daf-16* pathway	↑		(36)
	D. melanogaster	Promotes sustained physical performance and stress resistance	↑	↑	(37)
Cherries	*C. elegans*	Enhanced mitochondrial function and DAF-16 pathway	↑	↑	(38)
	C. elegans	Acts as a calorie restriction mimetic	↑	↑	(39)
Broccoli	*D. melanogaster*	SOD and CAT activity	↑		(20)
	D. melanogaster	CuZnSOD, MnSOD and catalase activities	↑		(40)
Grape skin	*D. melanogaster*	Activation of mitophagy in Parkinson's disease model	↑	↑	(41)
	Mice	Elevated *sirt1* mRNA expression		↑	(42)

lifespan and healthspan extension properties of foods in various organisms (Table 1)

Berries

The effects of blueberry extract on lifespan have been evaluated in *C. elegans* and *D. melanogaster* models. Blueberries are rich in anthocyanidins and proanthocyanidins, known for their potent antioxidant activity. These components extended the lifespan of *C. elegans* via antioxidant activity, CaMKII pathway regulation and increased thermotolerance[10]. A blueberry extract containing 49·2% cyanidin-3-*O*-glu and 20·1% petunidin-3-*O*-glu extended the lifespan of *D. melanogaster* by approximately 10% by enhancing the gene expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT)[11]. Among berries, cranberries are the most well studied in lifespan research. In *C. elegans*, cranberry extract extended the lifespan of the organism by increasing the transactivity of hsf-1[12], a protective factor against thermotolerance and Aβ toxicity. In *D. melanogaster*, sod1/2 expression levels were increased[13] and oxidative stress was reduced[14,15] by cranberries, resulting in a lifespan extension. DAF-16 is a key factor in the daf-2/IlS (insulin/IGF-1 signalling) signal transduction system and is the primary transcription factor involved in the regulation of lifespan[16]. Nrf2/Skn-1 signalling is involved in oxidative stress tolerance[17]. Raspberry extract extended the lifespan of *C. elegans* by alleviating oxidative stress via the up-regulation of the SKN-1/Nrf-2 pathway and increased DAF-16 translocation to the nucleus[18,19].

Green tea

Studies of the effects of green tea extract on lifespan have mainly been conducted in *D. melanogaster*. Reproductive potential in *D. melanogaster* was inhibited by green tea extract, mainly due to the increased activity of antioxidant enzymes, such as SOD and CAT[20] and the restriction of iron absorption[21]. These findings support the beneficial effects of green tea extract. In another study, SOD and CAT activity increased, whereas lipid hydroxides levels decreased, in response to green tea extract; however, there was no effect on lifespan[22]. In mouse experiments, green tea extract improved the mid-life (4 month) survival of UM-HET3 female mice, with no significant differences from the controls in terms of locomotor activity[23]. Overall, more data are needed to evaluate the effect of green tea extract in mice and other species.

Cocoa

When *C. elegans* was treated with cocoa suspension, ageing-related decreases in neuromuscular function, learning deficits and memory loss were improved, and the mean and median lifespan was prolonged. However, there was no effect on the maximal lifespan[24]. On the other hand, in *D. melanogaster*, cocoa extended the lifespan via antioxidant and metal chelating

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effects under excess heavy metals[25]. Cocoa polyphenol extract (total polyphenol content 34%) orally administered to rats at a dose of 24 mg/kg/d for 1 year for 15–27 months delayed age-related brain damage. In addition, it extended the lifespan by approximately 11%[26]. The composition of polyphenols was 88·5% procyanidins, including 0·21% anthocyanins, 10% epicatechin, 1% epicatechin gallate and 0·5% catechin. These results suggested that procyanidins in cocoa are related to its beneficial effects on lifespan.

Black tea

Black tea containing 60% theaflavins increased the survival rate and extended the lifespan of *D. melanogaster* through a decrease in LPO levels and the partial up-regulation of SOD1 and CAT under oxidative stress[27]. Water black tea extract also increased resistance to osmotic stress, heat shock and UV irradiation[28]. In addition, ROS was decreased due to an increase in the activity of the antioxidant enzyme glutathione peroxidase (GSH-PX). Nevertheless, there was no effect on the lifespan extension of *C. elegans*.

Orange

The predominant phenolic compound in orange extract obtained with 80% acetone was hesperidin. In *C. elegans*, orange extract effectively prolonged the lifespan via the reduction of the MDA content, improvement of SOD and CAT activity, increases in *daf-16*, *sod-3*, *gst-4*, *sek-1* and *skn-1* expression, and a decrease in *age-1* expression[29]. Orange peel extract also effectively prolonged the lifespan of *D. melanogaster* via the regulation of locomotor performance, memory index, antioxidant status and enzyme activities of cholinesterase and monoamine oxidase. In addition, DNA damage by free radicals was also prevented[30,31].

Apple

Apple polyphenol extracts increased the lifespan of *D. melanogaster* by 10% by increasing levels of genes encoding the endogenous antioxidant enzymes SOD1, SOD2 and CAT and downregulating methuselah (MTH)[32]. In *C. elegans*, apple polyphenol extracts improved mean lifespan by 39% and maximal lifespan by 25%. In addition, they enhanced resistance against heat shock, UV irradiation, *Pseudomonas aeruginosa* infection and paraquat stresses[33]. Moreover, combined treatment with apple and blueberry extract exerted a synergistic effect on lifespan (resulting in a 34% extension) compared with the effects of single treatment. The effects on lifespan were mediated by the regulation of the anti-ageing-related gene *DAF-16* and insulin signalling[34].

Other foods

In addition, the concentration range of 2·5–5 mg/mL ethanol extract of pomegranate was effective in prolonging the lifespan of *C. elegans*[35]. Moreover, pomegranate juice extended the lifespan of the organism by 56% by regulating the DAF-16 pathway[36]. In *D. melanogaster*, the lifespans of males and females were extended by 18% and 8%, respectively, through the promotion of continuous physical activity and improvement of free-radical-induced stress[37]. Tart cherry extracts extended lifespan in *C. elegans* via their calorie restriction mimetic function and the regulation of the DAF-16 pathway[38,39]. Broccoli increased survival time in *D. melanogaster* exposed to hydrogen peroxide by reducing lipid peroxides and increasing CuZnSOD, MnSOD and CAT activities[20,40]. When grape skins (pomace) were fed to *D. melanogaster*, an animal model for Parkinson's disease, after wine fermentation, muscle degeneration was suppressed, and the lifespan was extended[41]. Grape skin extracts partially improved the mitochondrial respiration rate with minor effects on memory and ATP levels in aged mice[42].

Studies of the effects of food extracts on lifespan or healthspan have focused on *C. elegans* and *D. melanogaster*. Lifespan studies in mice were limited to grape skin, cocoa and green tea. However, the most well-studied berries have never been evaluated using mice. Therefore, it is necessary to verify the efficacy observed in *D. melanogaster* and *C. elegans* using mice in the future and to obtain scientific evidence for the use of food to promote healthy ageing using cohort studies.

Phytochemicals that may extend lifespan and healthspan

Foods contain various ingredients that can be beneficial to human health, including phytochemicals. We evaluated trends in research on phytochemicals present in foods that prolong healthspan (Table 2).

Resveratrol

Resveratrol is a representative phytochemical that has attracted much attention as an anti-ageing functional substance since it was first introduced as an activator of NAD^+-dependent histone deacetylase (sirtuin), a lifespan regulator in metazoans[43,44]. Subsequent studies on resveratrol have suggested that it promotes lifespan extension via the activation of autophagy, an essential mechanism for maintaining cell homeostasis, in a Sirtuin-1-dependent manner[45]. On the other hand, in an experiment using *C. elegans*, resveratrol did not relieve oxidative stress or extend the lifespan under normal conditions. However, it prolonged the lifespan of *C. elegans* under oxidative stress conditions[46]. Resveratrol induces alterations in the transcription profiles of mice fed a high-calorie diet that are similar to those in mice fed a restricted diet. Resveratrol increased insulin sensitivity, decreased insulin-like growth factor-1 (IGF-1) and improved AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) and motor function compared with control mice. In addition, resveratrol significantly increased the survival rate of middle-aged obese mice[47]. In an experiment with SAMP8 mice, an Alzheimer's model, resveratrol also extended the lifespan by activating AMPK and pro-survival pathway, such as that of sirtuin1 (SIRT1)[48]. As a SIRT1 activator, resveratrol also extended the lifespan of diabetic mice. Only 10% of the mice fed resveratrol died, while 33% of the mice in the control group died before the study was terminated[49]. In SOD (G93A) mutant

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Table 2. Phytochemicals that promote lifespan and healthspan

Phytochemicals	Models	Major molecular mechanism	Lifespan	Healthspan	References
Resveratrol	*D. melanogaster* and *C. elegans*	*Sir2* (surtuin orthologue) activation	↑		(43)
	C. elegans	*Sir*-2·1 (surtuin orthologue) activation	↑		(44)
	C. elegans	*Sir-2·1*-mediated autophagy activity	↑		(45)
	C. elegans	Ameliorated oxidative stress	↑		(46)
	Mice	Increased the survival rate of middle-aged obese mice	↑	↑	(47)
	Mice	Increased insulin sensitivity, AMPK and PGC1a	↑	↑	(48)
	Mice	Activation of AMPK and SIRT1 pathways	↑	↑	(49)
	Mice	SIRT1 activator	↑		(50)
	Mice	Caloric restriction mimetic by resveratrol			(51)
	Cohort study	Serum CRP, IL-6, IL-1β and TNF expression			(52)
Quercetin	*C. elegans*	Reduced ROS accumulation and *daf-16* pathway	↑		(53)
	C. elegans	Led to translocation of *daf-16* into the nucleus	↑		(54)
	C. elegans	*Daf-16* is not obligatorily required for longevity	↑		(55)
	C. elegans	Activation of p38MAP kinase and CaMKII	↑		(56)
	C. elegans	Activation of *sir-2·1* and *daf-12*	↑		(57)
	C. elegans	Activation of HSF-1, ILS pathway and MAPK pathway	↑		(58)
	Mice	Improved the healthspan of physiologically ageing mice; however, lifespan was not prolonged		↑	(59)
Curcumin	*D. melanogaster*	Increased superoxide dismutase activity	↑		(60)
	D. melanogaster	Expression of *mth*, *InR* and *JNK*	↑		(61)
	C. elegans	Expression of *Osr-1*, *sek-1*, *mek-1*, *unc-43*, *sir-2·1* and *age-1*	↑	↑	(62)
	Mice	Lifespan of genetically heterogeneous mice			(23)
EGCG	*C. elegans*	Attenuates decline of pharyngeal pumping rates		↑	(64)
	C. elegans	AAK-2, SIR-2·2 and DAF-16-dependent redox signalling	↑	↑	(65)
	Mice	FoxO3a and SIRT1	↑	↑	(66)
	Mice	Affects muscle function rather than cognition	↑	↑	(67)
	Mice	AMPK, SIRT3, SIRT5 and autophagy activity	↑	↑	(68)
Spermidine	*D. melanogaster* and *C. elegans*	Inhibition of HAT activity and autophagy activation	↑		(69)
	D. melanogaster	Increased autophagy-dependent resistance to neurotoxic agents	↑	↑	(70)
	Mice	Enhanced cardiac autophagy and mitophagy	↑	↑	(71)
Caffeine	*C. elegans*	Up-regulation of antioxidant genes	↑		(72)
Ursolic acid	*C. elegans*	Lowered ROS and increased serotonin receptors	↑	↑	(73)
	C. elegans	Reduced ROS generation and *dop1* and *dop3* gene expression	↑	↑	(74)
Baicalein	*C. elegnas*	Activation of the Nrf2/SKN-1 signalling pathway	↑		(75)
	C. elegans	Increases stress resistance and lifespan in *C. elegans* via SKN-1	↑	↑	(76)
Withanolide A	*C. elegans*	Insulin/IGF-1 signalling	↑	↑	(77)
	C. elegans	Insulin/IGF-1 signalling	↑		(78)
Astaxanthin	*C. elegans*	Insulin/IGF-1 and TOR signal pathways involved in autophagy	↑		(79)
Caffeic acid	*C. elegans*	Insulin/IGF pathway	↑	↑	(80)
Tyrosol	*C. elegans*	*hsf-1*, *daf-2* and *daf-16* pathway	↑	↑	(81)
Myricetin	*C. elegans*	Prevention of oxidative stress and DAF-16 activation	↑	↑	(82,83)
Sesamine	*C. elegans*	Inhibition of Aβ oligomerization	↑		(84)
	C. elegans	Activation of *sir-2·1*, *daf-15* and *aak-2* pathways	↑		(85)

mice used as a model for amyotrophic lateral sclerosis, the effect of dietary restriction by resveratrol did not influence neurodegenerative diseases or lifespan. These results could be explained by the administration period of resveratrol, which was as short as 90 d[50]. In addition, there was no significant increase in survival rate in male and female UM-HET3 mice; in the same experiment, rapamycin improved the average survival rate by 10% for males and 18% for females[51]. A cohort study that followed urinary resveratrol metabolite concentrations for 9 years found no significant association between resveratrol levels in individuals consuming a Western diet and population health status or mortality risk[52]. Many lifespan studies have focused on resveratrol. However, mouse experiments and cohort studies have yielded inconsistent results regarding the association between resveratrol and lifespan. Therefore, human clinical trials are needed to determine whether resveratrol promotes lifespan extension.

Quercetin

Many studies have evaluated lifespan extension in *C. elegans* by quercetin under thermal stress. The effects of quercetin are mediated by the increased nuclear translocation of daf-16 and inhibition of ROS accumulation[53,54]. However, daf-16 may not be necessary for quercetin-mediated longevity and stress resistance, as a daf-16 mutant strain not only showed a lifespan extension of 15% but also showed resistance to thermal and oxidative stress. Therefore, other genes are likely to be involved in the regulation of lifespan[55]. In addition, quercetin prolongs lifespan by activating unc-43 (CaMKII), sek-1 (MAPKK)[56], Sir-2·1, co-activator MDT-15[57] and HSF-1 via the regulation of insulin-like and p38-MAPK pathway signalling[58]. A low concentration (0·125 mg/kg) of quercetin administered to 14-month-old C57BL/6J male mice weekly for 8 months had no effect on lifespan. However, hair loss, blood sugar and bone

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mineral density were improved. Regarding exercise ability, there was no effect on grip strength; however, there was a significant improvement effect on treadmill and rotarod performance[59]. In addition, retrotransposable element (RTE) activity, which increases with age, can promote inflammatory ageing. However, inhibiting RTE activity by quercetin in ageing mouse tissues can affect heterochromatin stabilization, increasing the healthspan of mice.

Curcumin

Curcumin lowers MDA in *D. melanogaster*, increases the activity of SOD, an antioxidant enzyme, and regulates the expression of ageing-related genes (*mth*, *InR* and *JNK*)[60,61]. In *C. elegans*, *osr-1*, *sek-1*, *mek-1*, *unc-43*, *sir-2·1* and *age-1* have been identified as ageing-related genes required for curcumin-mediated longevity[62]. Many studies have evaluated the preventive effects of curcumin in mouse models of diseases; however, studies of its effect on lifespan are rare. Curcumin was administered to genetically heterogenous mice from 4 months of age to investigate its effect on lifespan or healthspan. As a result, curcumin did not have a significant effect on the lifespan of males or females[23]. It is thought that curcumin will improve longevity and healthspan by activating autophagy, suppressing cellular senescence, inhibiting inflammatory SASP and changing the intestinal microflora in a beneficial direction[63]. However, there is no direct evidence for improvements in mouse lifespan and healthspan.

EGCG

EGCG increased the pharyngeal pumping rate of *C. elegans* but did not affect lifespan[64]. Survival was increased by 60% via aak-2, sir-2·2 and daf-16-dependent redox signalling under lethal conditions caused by oxidative stress[65]. Therefore, EGCG did not increase the lifespan of *C. elegans* but conferred resistance to oxidative stress. In another experiment, rats were provided drinking-water containing EGCG until they died. As a result, lifespan was extended by the inhibition of NF-κB signalling and activation of FOXOa and SIRT1. In addition, ageing-related inflammation and oxidative stress were improved in the liver and kidney[66]. In an ageing mouse experiment, EGCG increased the survival rate, although it did not improve cognitive ability or muscle function in ageing mice[67]. EGCG significantly increased DNA damage, cell cycle inhibitors, inflammatory markers, senescence-related secreted phenotype regulators, AMPK/AKT signalling, SIRT3/5 expression and autophagy markers in a study of cellular ageing, inflammatory ageing, immune ageing and intestinal bacterial imbalance at four timepoints. Therefore, several deleterious effects of ageing could be attenuated[68].

Spermidine

Spermidine inhibited histone acetyltransferase (HAT) activity in *D. melanogaster* and *C. elegans* and increased the expression of genes related to autophagy, resulting in lifespan extension[69]. In addition, the survival rate and locomotor ability of *Drosophila* were increased by increasing resistance to paraquat-induced toxicity in an autophagy-dependent manner[70]. Spermidine is one of the few compounds studied in mice. Lifespan was extended through cardiovascular protection, prevention of cardiac hypertrophy and maintenance of diastolic function by enhancing autophagy and mitophagy[71].

Other phytochemicals

Caffeine[72] and ursolic acid[73,74] extend lifespan in *C. elegans* by increasing the expression of antioxidant genes and reducing ROS levels. Baicalein also extends the lifespan of *C. elegans* by activating Nrf2/Skn-1 signalling, which is associated with oxidative stress resistance[75,76]. Withanolide A[77,78], astaxanthin[79] and caffeic acid[80] extend lifespan by regulating the insulin-like signalling (IlS) pathway. Compounds that directly mediate DAF-16 are tyrosol[81] and myricetin[82,83]. Sesamine extends lifespan by alleviating β-amyloid (Aβ)-induced defects in *C. elegans*[84]. In addition, lifespan was extended by the regulation of the *sir-2·1* (SIRT1), *daf-15* (Raptor) and *aak-2* (AMPK) pathways, which are related to caloric restriction, oxidative stress and the TOR pathway[85]. A recent study also suggested that several phytochemicals suppress degenerative diseases and contribute to longevity through the vitagene network[86]. Vitagenes, a group of genes that contribute to preserving cellular homeostasis in stress conditions, encode for heat shock proteins (Hsp) 70, Hsp60, haem oxygenase-1 (HO-1), the thioredoxin system and sirtuins[87]. Carnosic acid found in rosemary activates the vitagene system through Keap1/Nrf2/ARE pathway[88]. In addition, sulforaphane found in broccoli activates vitagenes by activating Nrf2 and enhancing the gene expression of HO-1, a target gene of Nrf2[89,90]. These effects of phytochemicals on vitagenes contribute to suppressing the alteration of cells and preventing brain damage[86]. However, the phytochemicals enhancing the vitagene network are not fully investigated. Therefore, additional studies are needed to enhance the understanding of the effects of vitagene-activating foods and their components on the healthspan of organisms.

Clinical studies

Clinical studies have mainly focused on caloric restriction, time-restricted feeding, macronutrient compositions and low-carbohydrate and ketogenic diets. In addition, a cohort study has revealed that a diet containing abundant beans, whole grains and nuts and relatively little red or processed meat can increase the average lifespan by more than 10 years[91]. However, exercise, fasting and calorie restriction are the most frequently performed interventions in clinical studies of ageing, even at ClinicalTrial.gov, a database of private and publicly funded clinical studies conducted worldwide. Resveratrol was the most common phytochemical in these studies. In a clinical study of thirty-nine healthy men and postmenopausal women (45–74 years old) randomized to receive a placebo ($n = 19$) or curcumin at 200 mg/d ($n = 20$) for 12 weeks, motor and cognitive function were not improved by curcumin supplementation. These findings support the view that the addition of curcumin to a regular diet does not further improve motor or cognitive performance in an ageing population. However, it has been suggested that curcumin may improve these functions in

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groups with more significant impairment than that of the study population, including adults over 75 years of age or patients with clinical disabilities. Therefore, further research on this topic is needed. A cohort study has also suggested that spermidine-rich food intake is highly correlated with survival and lifespan[92].

Conclusions

Preventing diseases and improving lifespan represent distinct aims. Despite numerous studies of the efficacy of various foods in preventing diseases, sufficient evidence for the improvement of lifespan has not yet been obtained. Although it is still too early to suggest foods that promote lifespan, research in this area has clearly established that an appropriate diet is essential for maintaining healthy ageing. In other words, although pre-clinical studies of food extracts and phytochemicals are ongoing, it is ultimately necessary to collect scientific evidence about the specific foods or diets able to maintain healthy ageing through clinical studies (intervention trials) in the future. Currently, the lifespan of foods is focused on *C. elegans* and *D. melanogaster*. Although studies on mice are limited because they are costly and time-consuming, more research on the healthy lifespan of mice needs to be secured, and ultimately, it is necessary to search for methods that can be applied to humans in the future.

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