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Effect of Green Tea and Its Polyphenols On the Lifespan of Model Organisms: A Systematic Review

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Abstract
Green tea contains phenolic compounds such as catechins and theanine that are known to exert positive effects to health in various organisms. The aim of this review is to determine the effect of green tea on the lifespan on healthy model organisms. PubMed and Scopus databases systematically searched according to predefined eligibility criteria by three reviewers. The initial 400 titles were screened for duplicates. After exclusion of duplicates, review papers, human studies, *in vitro* studies and studies using unhealthy organisms, a total of 29 research articles were assessed. The articles selected reported on models namely *Caenorhabditis elegans* (n=9), rodents (mice and rats, n = 8), *Drosophila melanogaster* (n = 11) and African honeybees (n = 1). In most studies, green tea extracts and catechins significantly increased the mean and median lifespan of the organisms. Generally, discrepancies of results within the same model organism were due to differences in the species, gender, sample size and experimental conditions used. The reviewed studies presented evidence that green tea and its constituents influence the lifespan of different healthy organisms. The effects of green tea are attributed to multiple components present in the tea. This is supported by various findings that reported modulation of lifespan when whole green tea extracts and isolated compounds were used.

Keywords: *Caenorhabditis elegans*, *Camellia sinensis*, catechins, mice, rats, honeybees

INTRODUCTION

Green tea is a popular beverage worldwide [1]. Produced from the leaves of the *Camellia sinensis*, this plant is mainly grown in tropical and subtropical regions. Research has shown that the main components of green tea that are associated with health benefits are the catechins. The four main catechins found in green tea are epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG)[2]. Of these catechins, EGCG is the most abundant in green tea and thus it has been used in most of the previous researches. Catechins are phenolic compounds present in green tea which has been claimed to be responsible for the antioxidatant activities of green tea [3]. Besides catechins, various flavonols, gallic, coumaric and caffeic acids, as well as the purine alkaloids, theobromine and caffeine are also found in this tea.

The richness of compounds present in green tea has exerted many positive outcomes of this tea. Intriguingly, the beneficial effects of green tea have not only been established at the *in vitro* level but supplementation of green tea in humans has also shown consistent results. Among the reported benefits of green tea include anticarcinogenic [4], antimicrobial [5], anti-inflammatory [6], antioxidant [3], [7], preventive of cardiovascular disease [8] and maintenance of oral health [9] as well as body weight [10].

To further establish the advantages of the tea, a possible influence of green tea on longevity has been studied in various types of animal models over the recent years. However, it remains unclear whether this tea can prolong or, on the contrary, decrease lifespan. The different outcomes could be due to the complexity of genotype of model organisms used, dosage of green tea supplementation or perhaps the discrepancy in the constituents of green tea since it is a natural product. Therefore, the purpose of this review is to summarize the results of studies on green tea supplementation and lifespan in model organisms with biological complexity to address the extent of lifespan modulation by green tea in single cell organisms, nematodes, flies, mice and rats.

METHODS

A systematic review of the literature was conducted to identify relevant studies about the effects of green tea on the lifespan of model organisms. A comprehensive database search in health science journals was conducted, in Scopus and PubMed for relevant research articles published up to April 2017.

The selection of papers to be included in this review took place in three phases by three reviewers. The first phase was the exclusion of papers that did not fulfil the inclusion criteria, based on the title, and removing duplicates. To be included, studies had to report the effect of green tea or its compounds on the lifespan in model organisms and healthy organisms. Titles were excluded if the studies were related to human studies, unhealthy organisms, cell culture, reviews, news, letter, editorials. The second phase involved screening the abstracts of the remaining titles, and excluding the papers that did not meet the inclusion criteria. The final phase was reading full papers from the remaining collection, and excluding publications that failed to meet the inclusion criteria. Finally, data were extracted from the papers that have been agreed upon by the same reviewers.

Data extraction was performed independently using a standardized form. The following data were recorded from the studies:

1) Species of the organism used in the research;
2) Sample size per treatment;
3) Type of extracts used;
4) Dose of treatment;
5) Initiation of treatment
6) Condition of the treatment;
7) Mean lifespan of the organism;
8) Maximum lifespan of the organism;
9) Authors of the study.

RESULTS AND DISCUSSION

Study selection

From the initial search from Scopus and PubMed, a total of 400 titles were generated and screened for duplicates (Figure 1). Exclusion criteria were also screened from the list titles, such as indications of review papers, human studies, *in vitro* studies and studies using unhealthy organisms. Following this, 249 titles were excluded from the study, leaving 151 eligible titles. Abstracts of these research titles were screened with the same exclusion criteria stated previously, excluding a total of 60 abstracts. Then, 91 full research papers of the remaining abstracts were screened using the inclusion and exclusion criteria mentioned in the methods section. Ultimately, data were extracted from 29 research articles.

Based on the studies included, the outcomes were classified into four major organisms; *Caenorhabditis elegans*, *Drosophila melanogaster*, rodents (mice and rats) and African honeybees. A total of 29 studies fulfilled the eligibility criteria. Most of the studies were reported in the second millennium except for two. All papers reported on longitudinal studies where the lifespan and survival of organisms was determined following treatment with green tea extracts or its polyphenols.

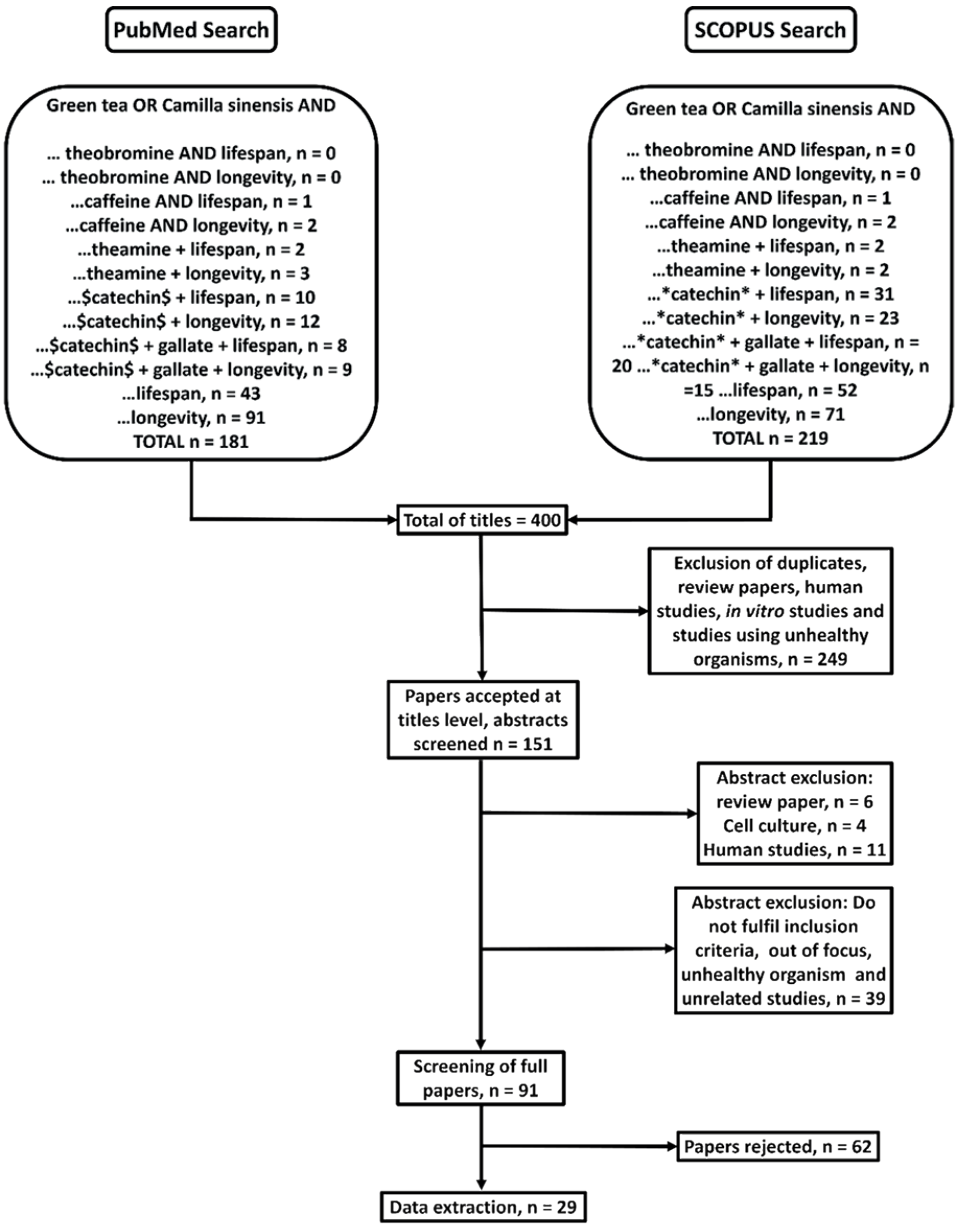

Figure 1. Flow of literature search

Lifespan of C. elegans

A total of nine studies used *C. elegans* as a model for the determination of lifespan modification by green tea and its polypohenol extract [11]-[19]. Table 1 highlights the findings of the selected studies. All studies used the wild-type laboratory strain, Bristol (N2) *C. elegans*, and grew the worms in nematode growth medium (NGM) seeded with *Escherichia coli* either in solid [11], [13], [14], [16], [17] or liquid [15] phases. Only three studies employed liquid mediums (S-medium, S basal buffer and liquid NGM) to grow the worms [12], [15], [19].

A total of three studies determined the effect of epigallocatechin-3-gallate (EGCG) on the lifespan of *C. elegans* [11], [14], [15]. Studies which used doses of EGCG of less or equal to 100 μM was found to have no significant effects on the lifespan of *C. elegans* [11], [14]. On the other hand, Abbas and Wink (2009)[12] reported that daily administration of 220 μM EGCG successfully increased the mean lifespan of *C. elegans* by 10.14%.

Saul et al. (2009; 2011)[13], [16] reported the effects of catechin on the lifespan of *C. elegans* in two separate reports. In these studies, similar culture conditions were employed where L4 larvae N2 strains were treated with catechin and maintained at 20oC on NGM seeded with *E. coli* feeding strain OP50. The concentrations of catechin used were also similar except for the later study which extended the trial to higher doses of 400 and 800 μM [16]. In contrast, Surco-Laos et al. (2012)[17] reported no effect of catechin and epicatechin treatments on the lifespan of *C. elegans*. In the same study, treatment with the methylated forms of catechin such as 4'-O-methylepicatechin and 3'-O-methylepicatechin at 200 μM respectively were reported to increase the lifespan of *C. elegans* as compared to control.

Only one study reported on the use of a whole green tea extract as treatment in the lifespan study. According to Murakami et al. (2015)[19], dried leaves were soaked in water at room temperature for 15 minutes, steamed and then centrifuged at 10,000g. The pellet was frozen at 40oC and dried to yield freeze-dried material. Tea extracts were prepared by boiling the freeze-dried material in water and then filtered followed by centrifugation. Lastly, the extracts were sterilized using a 0.2 microfilter. The tea extracts resulted in increased lifespan of *C. elegans* to a maximum of 25 days and 27 days at 0.2% and 1% volume/volume respectively.

The effect of L-theanine to lifespan of *C. elegans* was reported by one study [18]. L-theanine in this study was purchased from Sigma. Hence, the origin of the compound was not reported in the study. In this study, L-theanine extended the lifespan of *C. elegans* lifespan when applied at concentrations of 100 nM, as well as 1 and 10 μM.

Lifespan of Drosophila melanogaster

The data were extracted from 11 articles, published from 1993 to 2017 (Table 2). All studies used more than 100 flies per treatment, except for Si et al. (2017)[20] and Ortega-Arellano et al. (2011)[21], who used 30/40 and 50 flies, respectively; and Yang et al. (2013)[22] which did not state the sample size. In the research article, Si et al. (2011)[20] stated that 30 flies per treatment was used in the methods and materials section, as opposed to the figure caption, which stated that 40 flies per treatment was used. Most of the studies applied similar conditions, rearing the flies with conventional diet comprising of differing percentage of agar, yeast and sucrose. Li et al. (2008)[23] introduced lard in the diet, while Massie et al. (1993)[24] used yellow corn meal medium. All studies reared the flies at 25°C on a 24-h light dark cycle, except for Lopez et al. (2014)[25], which reared the flies in a 20°C environment.

Only one article reported the use of theanine on *D. melanogaster* [22], which had no effect of the lifespan of the flies. Most of the active compounds from green tea such as catechins [23], [26], epicatechin [21], [27] (Ortega-Arellano et al. 2011; Proshkina et al. 2016), epigallocatechin gallate (EGCG) [21], [28], significantly increased the mean lifespan. Others used extracts such as green tea extract [24], [29](Massie et al. 1993; Cui et al. 1999) and green tea polyphenols mixture [25], resulted in increased mean lifespan. Lopez et al. (2014)[25] reported no significant effect on mean lifespan of female flies by green tea polyphenols. Epicatechin at higher concentrations (0.5 μM and 1.0 μM for male flies, 1.0 μM for female flies) did not significantly increase the mean lifespan [27]. Two of the articles did not provide data for the mean lifespan [20], [30].

Three studies documented significant maximum lifespan increase by 0.1 mM epicatechin [20], 10 mg/ml EGCG [30] and 1 mg/ml green tea extract in female flies [29]; while four reported insignificant maximum lifespan changes by 10 mg/ml catechins [23], 1.0, 5.0 and 10.0 mg/ml catechins [26], 1 mg/ml green tea extracts in male flies [29] and 0.3, 0.5 and 1.0 μM epicatechin [27]. The rest of the publications did not report any data on maximum lifespan [21], [22], [24], [25], [28].

Lifespan of rodents (mice and rats)

Seven of the chosen articles contributed to the study of mice, and one study on Wistar rats (Table 3) [31]. All studies used different species of mice. Strong et al. (2013)[32] used 153 to 158 mice, which was the highest number used in their research, one study [33] did not mention of the sample size, one study used six mice [34], while the others used between 25 to 50 mice [31], [35]-[38].

Only two studies used EGCG [31], [34] while the others used green tea extracts [32], [33], [36], [38] and green tea polyphenols [35], [37]. Of all research reported, 25 mg/kg/day of EGCG significantly increased the lifespan of Wistar rats [31], while 115 ppm of the same compound have no effect on the median lifespan of C57BL/6 male mice [34]. Only one study that used green tea extract saw a significant increase in the mean lifespan [36], while the others reported no significant effect on the mice [32], [33], [38]. Green tea polyphenols treatment by Kitani et al (2004)[35] reported significant increase in the mean lifespan of the mice. In 2007, Kitani et al.[37] reported that polyphenols significantly reduced the lifespan of mice, using the same conditions they applied in the 2004 study [35].

Lifespan of African honeybees

Out of the 29 papers eligible for data extraction, only one paper recorded a study on African honeybees, *Apis mellifera scutellata* (Table 4) [39]. This study tested various concentration of EGCG (0.1, 0.3, 0.5 and 2.2 mM) on the survival of 100 bees per treatment. Treatment of the bees with 0.1 mM EGCG had no significant effect on the survival. Both the 0.3 mM and the 0.5 mM EGCG diets improved the percentage of survival, but not the highest concentration, where it significantly decreased the percentage of survival.

Table 1. Characteristics of studies on *C. elegans*.

Species	n	Extract	Dose	Initiation of treatment	Condition	Mean lifespan	Maximum lifespan	Study
Wild-type N2	383	Catechin	100 µM	L4 larvae	Solid nematode growth medium with *E. coli* at 20°C	18.21±1.05 days*	-	Saul *et al*. (2011)[16]
	564		200 µM			18.41±1.16 days*	-	
	289		300 µM			16.81±1.41 days*	-	
	307		400 µM			17.36±1.03 days*	-	
	296		800 µM			17.19±1.15 days*	-	
Wild-type N2	383	Catechin	100 µM	L4 larvae	Solid nematode growth medium with *E. coli* at 20°C.	18.21 days*	-	Saul *et al*. (2009)[13]
	564		200 µM			18.41 days*	-	
	289		300 µM			16.81 days*	-	
Wild-type N2	NA	EGCG	0.1 µg/ml, 1.0 µg/ml, 10.0 µg/ml	NA	Solid nematode growth medium with *E. coli* at 20°C.	No effect	-	Zhang *et al*. (2009)[14]
Wild-type N2	216	Catechin,	200 µM	L1 larvae	Solid nematode growth medium with *E. coli* at 20°C.	17 ± 0.4 days	28.6 ± 2.1 days	Surco-Laos *et al*. (2012) [17]
	213	Epicatechin	200 µM			17.5 ± 0.6 days	31.2 ± 2.3 days*	
	199	4'-*O*-methylepicatechin	200 µM			19.6 ± 0.5* days	31± 1.4 days*	
	210	3'-*O*-methylepicatechin	200 µM			18.6 ± 0.5* days	29.2 ± 2.8 days*	
Wild-type N2	100	EGCG	25 µM	Day-4 adult	Solid nematode growth medium with *E. coli* at 20°C	13±1.6 days	22±2.0 days	Brown *et al*. (2006)[11]
Wild-type N2	10	*Camellia taliensis* and C. sinensis L-theanine	0.2 % v/v	Day-4 adult	S basal buffer with *E. coli* at 20°C	19.6 days*	25 days*	Murakami *et al*. (2015) [19]
			1% v/v			20.5 days*	27 days*	
Wild-type N2	60	EGCG	100 µM	Adult worms	Liquid nematode growth medium containing solvent control (0.1% DMSO), at 20°C	35.4±2.0 days*	53.3±1.5 days*	Bartholome *et al*. (2010) [15]
	60	Epicatechin	100 µM			34.0±1.2 days*	52.0±2.7 days*	
Wild-type N2	100	EGCG	220 µM	3 days old adult	S-medium consisting *E. coli* maintained at 20°C	26.49±0.59 days	35*	Abbas *et al*. (2009)[12]
Wild-type N2	385	L-theanine	0.1 µM	Day-4 worms	Solid nematode growth medium with *E. coli* at 20°C	22.9±0.2 days*	26.0±0.4 days	Zarse *et al*. (2012)[18]
	378		1 µM			22.8±0.1 days*	25.5±0.2 days	
	365		10 µM			22.6±0.6 days*	25.5±0.6 days	

* significant increase compared to control, d significant decrease compared to control. NA: Not available

Table 2. Characteristics of studies on *D. melanogaster*.

Species	n	Extract	Dose	Initiation of treatment	Condition	Mean lifespan	Maximum lifespan	Study
Wild-type	30/40	Epicatechin	0.1mmol/L	-	Basal diet at 25°C, 12-h day/night cycle	NA	Increased lifespan*NA	Si *et al*. (2011)[20]
Wild-type	120	EGCG	10 mg/ml	-	Basal diet at 25°C, 12-h day/night cycle	NA	78 days*	Wagner *et al*. (2015) [30]
Wild-type	200 200	Catechins	10 mg/ml	-	Basal diet at 25°C 5% lard 10% lard	29±2.3 days* 24±1.8 days*	50 days 40 days	Li *et al*. (2008)[23]
Wild-type	200	Catechins	1 mg/ml 5 mg/ml 10 mg/ml	2-day-old	Basal diet at 25°C on 12 h light/dark cycle	54±1.9 days* 55±2.0 days* 59±2.8 days*	79 days 79 days 79 days	Li *et al*. (2007)[26]
Wild-type	200	Green tea extract	1 mg/ml Chinese medicine containing green tea extract	-	Basal diet with Chinese medicine containing green tea extract at 25°C	Male 52.5±16.6 days* Female 68.0±21.8 days*	83.0±8.3 days 97.0±3.1 days*	Cui *et al*. (1999)[29]
Wild-type	139-220	EGCG	1 mM 10 mM	New eclosed adult flies	Basal diet at 25°C on 12 h light/dark cycle	Female: Increased median lifespan Male 47±11.3 days[d] Female 48±15.4 days[d] Male 43±11.8 days[d]	-	Kayashima *et al*. (2015)[28]
Wild-type	120	Green tea polyphenols consisting 47% EGCG	10 mg/ml	-	Dietary restriction by decreasing concentration of yeast at 22±1.0°C	Male Increased lifespan* Female No effect	-	Lopez *et al*. (2014) [25]
Wild-type	100	Green tea extract	-	One-day-old adult	Yellow corn meal medium. Basal diet at 25°C on 12 h light/dark cycle	64.5±13.2 days*	-	Massie *et al*. (1993) [24]
Wild-type (female)	50	Epicatechin EGCG	0.1 mM 0.1 mM	2- 3 days after eclosion	Basal diet at 25°C on 12 h light/dark cycle and treated with paraquat and polyphenols for 15 days.	Increased lifespan*	-	Ortega-Arellano *et al*. (2011) [21]
Wild-type	100-200	Epicatechin	Long-term treatment 0.3 µM 0.5 µM 1.0 µM Long-term treatment 0.3 µM 0.5 µM 1.0 µM 10-day treatment 1.0 µM 30-40-day treatment 1.0 µM	New eclosed adult flies	Basal diet at 25°C on 12 h light/dark cycle	(Only results of second replicate is presented here) For the detection of short-term treatment effects, epicatechin was added during first 10 days of an imago life, as well as at the age of 30–40 days Male 37.3±1.0 days* 50.7±1.1 days 41.1±1.5 days Female 52.3±1.0 days* 61.8±1.0 days* 57.4±1.1 days 7-8%* median lifespan (male and female) 16%* median lifespan (female)	64 days 78 days 93 days 97 days 96 days 89 days	Proshkina *et al*. (2016)[27]
Wild-type	NA	L- Theanine	0.001 mg/ml, 0.1 mg/ml, 10 mg/ml	40 day old	Flies were reared on a standard cornmeal agar medium at 25 °C on a 24-h light dark cycle.	No changes	-	Yang *et al* (2013)[22]

* significant increase compared to control, d significant decrease compared to control. NA: Not available

Table 3. Characteristics of studies on rodents (mice and rats).

Species	n	Extract	Dose	Initiation of treatment	Condition	Lifespan	Study
Male C57L/6JNia mice	50	Green tea polyphenols	80 mg/ml	13 months old	Normal diet	852.7±88.2 days* (mean lifespan)	Kitani *et al*. (2004)[35]
C57BL/6J male x SJL female hybrids	25	Green tea extract	7.2 mg/day	2 months old	Normal diet with formulated supplement	764.60 + 23.92 days* (mean lifespan)	Lemon *et al*. (2005)[36]
Male C57BL/6JHsd mice	50	Green tea polyphenols	80 mg/ml	13 months old	Normal diet	52.7 ± 88.2 days* (mean lifespan)	Kitani *et al*. (2007)[37]
Female ICR-CD1 mice	NA	Green tea extract	NA	16 months old	Diets consisting isoflavones and green tea	No effect	Baeza *et al*. (2010)[33]
Male C57BL/ 6 mice	6	EGCG	115 ppm	4 months old	Repeated fasting and refeeding in 24 hour cycles with blueberry, pomegranate, and green tea extracts	33.5 days* (median survival)	Aires *et al*. (2012)[34]
Male B6C3F1 mice	36	Green tea extract	931 mg/kg diet 99 mg /kg diet	12 months	Normal diet	No effect	Spindler *et al* (2013)[38]
UM-HET3 mice	153 to 158	Green tea extract	2000 mg/kg diet	4 months	Diet consisting extract mixed with purina	No effect	Strong *et al* (2013)[32]
Male Wistar rats	34	EGCG	25 mg kg/ day	4 weeks old	Normal diet	105 weeks (median lifespan)*	Niu *et al*. (2013)[31]

* significant increase compared to control, [d] significant decrease compared to control, NA: Not available

Table 4. Characteristics of studies on African honeybees.

Species	n	Extract	Dose	Initiation of treatment	Condition	Lifespan	Study
African honeybees (*Apis mellifera scutellata)*	100	Epigallocatechin-3-gallate	0.1 mM	freshly emerged bees	Diet consisting of 0.63 M sucrose solution	Not significant	Archer *et al*. (2014)[39]
			0.3 mM			Improved survival*	
			0.5 mM			Improved survival*	
			2.2 mM			Decreased survival[d]	

* significant increase compared to control, d significant decrease compared to control

DISCUSSION

C. elegans

C. elegans is a microscopic soil worm or nematode used frequently for research pertaining to survival because of its short lifespan. The nematode is usually grown on Nematode Growth Medium (NGM) seeded with *E. coli* OP50 and maintained at temperatures between 15-25°C. However, the differences in incubation temperatures affect the lifespan of *C. elegans* significantly where low temperatures are known to extend lifespan while high temperatures shorten it. Adult worms exposed to 15°C can live up to about 40 days while incubation at 25°C decreases the lifespan to about 25 days [40]. All the studies reported in this review incubated *C. elegans* at 20°C. Hence, most of the reported mean lifespan of *C. elegans* were within the range of lifespan expectancy except for the study done by Bartholome et al. (2010) [15]. In the study, lifespan of *C. elegans* was increased to 52 days and above when the worms were grown in liquid NGM containing solvent control (0.1% DMSO), EGCG or epicatechin 100 µM each. Liquid NGM is often used to grow large quantities of *C. elegans* [41]. Previously, liquid culture system has been found to minimize mechanical stress to *C. elegans* and results in extension of lifespan in *C. elegans* [42]. Two studies using S-mediums as culture conditions to determine the effect of EGCG and green tea extracts also reported slightly higher maximum lifespans of *C. elegans* as compared to other studies using solid NGM [12], [19].

A recent study reported that EGCG increases the lifespan of *C. elegans* by inducing AMPK/SIRT1/FOXO-dependent redox signaling module. Induction of these pathways leads to stimulation of mitochondrial biogenesis and restoration of mitochondrial function [43]. Results of *C. elegans* lifespan studies with EGCG treatment found in this review did not support the positive effects of the compound because all studies did not report any significant changes to the mean lifespan of *C. elegans* as compared to control. Though Bartholome et al. (2010)[15] reported an increase of mean lifespan of 20% and 15% in *C. elegans* with EGCG and epicatechin treatment respectively; no significant values were stated in the report. Elsewhere, the other studies on EGCG reported insignificant changes to mean lifespan of *C. elegans*. Supplementation of EGCG has been claimed to increase fat oxidation [44] and energy metabolism [45]. It has also been demonstrated that several long-lived *C. elegans* mutants increase their life span by decreasing

their metabolism [46], which agrees with the findings that higher metabolic rates may increase ROS production, which shortens the life span due to increased oxidative stress. Taken together, EGCG increases energy expenditure and concurrently scavenges free radicals that results in the worms having a normal life span.

Studies using catechin as treatments have produced inconsistent results to the lifespan of *C. elegans*. Treatment of catechin between 100 μM to 800 μM was found to increase the mean lifespan of *C. elegans* significantly in two separate reports [13], [16]. Similarly, Bartholome et al. (2010)[15] found elevated mean and maximum life span of *C. elegans* in the presence of epicatechin. In contrast, no enhancement of mean lifespan was found in nematodes treated with 200 μM catechin nor epicatechin in another study done by Surco-Laos et al. (2012)[17]. Only the maximum lifespan of worms was increased in the treatments with epicatechin and its methylethers in this study. According to Gruber et al. (2009[47]), discrepancies in the results obtained by different studies might be due to differences in the handling and biological and physical environments of the assays, as well as to artefactual observations. Thus, blinding studies and using sufficiently large number of worms is suggested to produce more reliable results.

L-theanine is an amino acid known to be contained in green tea. Concentration of L-theanine at micromolar has been found to extend lifespan of *C. elegans* in normal condition and increases its survival in the presence of stress. Though L-theanine is known to poses antioxidant properties [48], the effects of the compound on stress resistance and lifespan remains unknown.

D. melanogaster

Catechins is a group of compounds consisting of epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate (EGCG), constructed by a common backbone structure. In this review, all types of catechins demonstrate significant lifespan-extending ability in *D. melanogaster*. Catechins have phenolic hydroxyl groups that are able to stabilize the free radicals [49], contributing to its antioxidant property [50], hence the ability to extend lifespan. However, Kayashima et al (2015)[28] reported the significant shortened lifespan of the male flies. Based on results from the same publication, they concluded that EGCG was very effective at suppressing fat accumulation. This effect led to the exhaustion of stored caloric energy, thus the flies succumbed to a shorter lifespan.

Short term treatments of 1.0 μM epicatechin on *D. melanogaster* extended the median lifespan [27]. Epicatechins added to the diet during the first 10 days of an imago life resulted in 7-8% of the median lifespan for both male and female flies. However, addition of 1.0 μM epicatechin to the diet during 30-40 days of life only produced a positive effect of the female flies only (16%), as well as at the age of 30-40 days. The long-term treatment of 1.0 μM epicatechin did not significantly extended the lifespan, due to the negative effects of the epicatechin. Epicatechin, has a pro-oxidant property, which can lead the organism to undergo oxidative stress. The stress will damage the biomolecules such as DNA, lipids and proteins, which can also lead to mitochondrial dysfunctions. These events will ultimately force the cells to undergo apoptosis [27].

Concoction of the active compounds such as those in green tea extracts[24], [29] and green tea polyphenols [25] generally increased the mean lifespan of the flies. The benefits of these extracts can be attributed to the collective effects of the different compounds [49].

L-Theanine, another compound found in green tea, did not affect the lifespan of the flies [22]. The reason for this finding is still unknown, which contrasted with another study [18] that extended the lifespan of *C. elegans*.

Rodents (mice and rats)

All of the studies (Table 3) utilized mice, except for one, which used Wistar rats [31]. Treatment of green tea extracts on mice showed inconsistent results where some researchers reported increased mean and median lifespan with the treatment[34], [36], [37] (Lemon et al. 2005; Kitani et al. 2007; Aires et al. 2012) while a few studies reported no effects of the treatment to lifespan [32], [33], [38]. This discrepancy may be due to the differences in the species of mice used for the studies. Lemon et al. (2005) [36] proposed that the presence of other constituents in their green tea extracts such as vitamins, resulted in a complex of antioxidant activities, hence prolonging lifespan. However, green tea extracts were also reported to have no effect on the lifespan of the tested animals. Baeza et al. (2010)[33] conducted a preliminary research using green tea extract, hence concluded the doses of green tea administered was not high enough to affect the lifespan of the mice. Spindler et al. (2013)[38] found that the green tea extract had no effect on the lifespan of mice, contrary to findings in other studies. They concluded that the previous studies were more prone to false positive outcome, when using lower eukaryotes and weakened rodents. A research by Strong and colleagues in 2013[32], who used the most number of samples, also found no effect of green tea extracts on their animals. Their findings contradicted with other studies that tested green tea extract on mice [35]-[37] due to dissimilarities in the green tea used, and the strain of mice used.

Two studies tested green tea polyphenols on mice [35], [37]. Kitani et al. (2007)[37] reported that green tea polyphenol significantly increased the lifespan of male C57BL/6JHsd mice. However, their data did not support their conclusion. Contrary to the research by the same group in 2004 [35] which used male C57L/6JNia mice, green tea polyphenols significantly increased the lifespan. Though the exact mechanism for prolonged survival of animals was unclear, the prevention of aging disorder in the animals was attributed to the antioxidant properties of green tea polyphenols [37].

Aires et al. (2012)[34], the only study that tested EGCG on mice reported significant increase of median survival in mice. The study involved dietary restriction in mice, which resulted in the decline of cell stress and inflammation-related activity, postulated to be the underlying mechanism [34].

The ability of EGCG in reducing the median lifespan of Wistar rats is suggested to be attributed to the anti-inflammatory and antioxidant properties of EGCG [31]. In the study, EGCG significantly reduced the levels of malondialdehyde and reactive oxygen species, increased the activities of endogenous antioxidant enzymes superoxide dismustase and glutathione peroxidase, while also increased their respective mRNA levels.

African honeybees

Honeybees are the major pollinators of various types of plants [51]. Extension of lifespan of the bees is of interest to researches as they have great economic and ecological importance. Nutrition is the key determinant of honeybee survival[52], [53]. To test the effect of EGCG on the lifespan on these bees, Archer et al. (2014) [39]obtained A.m. scutellata colonies from University of Pretoria experimental

farm and incubated them at 34oC in constant darkness. Freshly emerged bees were caged and treated with 0.63 M sucrose solution and EGCG at multiple doses. Dead bees were removed from cages and survival was determined daily. To determine the consumption of diets, mass changes between provided experimental diets and retrieved diets after twenty-four hours were calculated. Intermediate EGCG doses (0.3-0.5 mM) were reported to improve the survival of bees, while a high dose (2.2 mM) reduced it. This negative effect may suggest that excessive consumption of antioxidants such as EGCG can disrupt optimal reactive oxygen species homeostasis and decrease survival of organisms [54].

The reviewed studies presented evidence that green tea and its constituents influence the lifespan of different healthy organisms. The effects of green tea are attributed to multiple components present in the tea. This is supported by various findings that reported modulation of lifespan when whole green tea extracts and isolated compounds were used.

REFERENCES

[1] H. Wang, H. D. Du, R. Y. Hu, Y. J. Qian, C. M. Wang, K. X. Xie, L. L. Chen, D. X. Pan, Z. Bian, Y. Guo, M. Yu, L. M. Li, and Z. M. Chen. 2018. Association between tea drinking and stroke in adults in Zhejiang province: a prospective study. Zhonghua Liu Xing Bing Xue Za Zhi. 39(9):1200-1205.

[2] Chacko SM, Thambi PT, Kuttan R and Nishigaki I. 2010. Beneficial effects of green tea: A literature review. Chin Med. 5:13-21.

[3] Yu F, Sheng J, Xu J, An X and Hu Q. 2007. Antioxidant activities of crude tea polyphenols, polysaccharides and proteins of selenium-enriched tea and regular green tea. Eur Food Res Technol. 225(5-6):843-848.

[4] Yang CS and Wang X. 2010. Green tea and cancer prevention. Nutr Cancer. 62(7):931-937.

[5] Reygaert WC. 2014. The antimicrobial possibilities of green tea. Front Microbiol.5(AUG):434.

[6] Singh R, Akhtar N and Haqqi TM. 2010. Green tea polyphenol epigallocatechi-3-gallate: inflammation and arthritis. Life Sci. 86(25-26):907-918.

[7] Yanagimoto K, Ochi H, Lee KG and Shibamoto T. 2003. Antioxidative activities of volatile extracts from green tea, oolong tea, and black tea. J Agric Food Chem. 51(25):7396-7401.

[8] Wolfram S. 2007. Effects of green tea and EGCG on cardiovascular and metabolic health. J Am Coll Nutr. 26(4):373S-388S.

[9] Narotzki B, Reznick AZ, Aizenbud D and Levy Y. 2012. Green tea: A promising natural product in oral health. Arch Oral Biol. 57(5) :429-435.

[10] Westerterp-Plantenga MS. 2010 Green tea catechins, caffeine and body-weight regulation. Physiol Behav. 100(1):42-46.

[11] Brown MK, Evans JL and Luo Y. 2006. Beneficial effects of natural antioxidants EGCG and α-lipoic acid on life span and age-dependent behavioral declines in Caenorhabditis elegans. Pharmacol Biochem Behav. 85(3):620-628.

[12] Abbas S and Wink M. 2009. Epigallocatechin gallate from green tea (Camellia sinensis) increases lifespan and stress resistance in Caenorhabditis elegans. Planta Med 75:216-221.

[13] Saul N, Pietsch K, Menzel R, Stürzenbaum SR and Steinberg CEW. 2009. Catechin induced longevity in C. elegans: From key regulator genes to disposable soma. Mech Ageing Dev. 130:477-486.

[14] Zhang L, Jie G, Zhang J and Zhao B. 2009. Significant longevity-extending effects of EGCG on Caenorhabditis elegans under stress. Free Radic Biol Med.46(3):414-421.

[15] Bartholome A, Kampkötter A, Tanner S, Sies H and Klotz L. 2010. Epigallocatechin gallate-induced modulation of FoxO signaling in mammalian cells and C. elegans: FoxO stimulation is masked via PI3K/Akt activation by hydrogen peroxide formed in cell culture. Arch Biochem Biophys. 501:58-64.

[16] Saul N, Pietsch K, Stürzenbaum SR, Menzel R and Steinberg CEW. 2011. Diversity of polyphenol action in Caenorhabditis elegans: Between toxicity and longevity. J Nat Prod. 74(8):1713-1720.

[17] Surco-Laos F, Dueñas M, González-Manzano S, Cabello J, Santos-Buelga C and González-Paramás AM. 2012. Influence of catechins and their methylated metabolites on lifespan and resistance to oxidative and thermal stress of Caenorhabditis elegans and epicatechin uptake. Food Res Int. 46(2):514-521.

[18] Zarse K, Jabin S and Ristow M. 2012. L-Theanine extends lifespan of adult Caenorhabditis elegans. Eur J Nutr. 51(6):765-768.

[19] Murakami A, Nesumi A, Maeda-Yamamoto M, Yamaguchi K, Yashima M, Miura M, Nakano T and Nekoshima K. 2015. Anthocyanin-rich tea Sunrouge upregulates expressions of heat shock proteins in the gastrointestinal tract of ICR mice: A comparison with the conventional tea cultivar Yabukita. J Food Drug Anal 23(3):407-416.

[20] Si H, Fu Z, Velayutham P, Babu A, Zhen W, Leroith T, Meaney MP, Voelker KA, Jia Z, Grange RW and Liu D. 2011. Dietary epicatechin promotes survival of obese diabetic mice and Drosophila melanogaster1-3. J Nutr 141:1095-1100.

[21] Ortega-Arellano HF, Jimenez-Del-Rio M and Velez-Pardo C. 2011. Life span and locomotor activity modification by glucose and polyphenols in Drosophila melanogaster chronically exposed to oxidative stress-stimuli: implications in Parkinson's disease. Neurochem Res. 36:1073-1086.

[22] Yang H, Li W, Yu H, Yuan R, Yang Y, Pung K, Li P, and Xue L. 2013. Physiological effects of L-Theanine on Drosophila melanogaster. Molecules. 18:13175-13187.

[23] Li YM, Chan HYE, Yao XQ, Huang Y and Chen ZY. 2008. Green tea catechins and broccoli reduce fat-induced mortality in Drosophila melanogaster. J Nutr Biochem. 19:376-383.

[24] Massie HR, Aiello VR and Williams TR 1993. Inhibition of iron absorption prolongs the life span of Drosophila. Mech Ageing Dev. 67:227-237.

[25] Lopez T, Schriner SE, Okoro M, Lu D, Chiang BT, Huey J and Jafari M. 2014. Green tea polyphenols extend the lifespan of male Drosophila melanogaster while impairing reproductive fitness. J Med Food. 17(12):1314-1321.

[26] Li YM, Yin H, Chan E, Huang Y and Chen ZY. 2007. Green tea catechins upregulate superoxide dismutase

and catalase in fruit flies. Mol Nutr Food Res. 51:546-554.

[27] Proshkina E, Lashmanova E, Dobrovolskaya E, Zemskaya N, Kudryavtseva N, Shaposhnikov M and Moskalev A. 2016. Geroprotective and radioprotective activity of quercetin, (-)-epicatechin, and ibuprofen in Drosophila melanogaster. Front Pharmacol. 7(DEC):505.

[28] Kayashima Y, Murata S, Sato M, Matsuura K, Asanuma T, Chimoto J, Ishii T, Mochizuki K, Kumazawa S, Nakayama T and Yamakawa-Kobayashi T. 2015. Tea polyphenols ameliorate fat storage induced by high-fat diet in Drosophila melanogaster. Biochem Biophys Reports. 4:417-424.

[29] Cui X, Dai X, Li W-B, Zhang B-L and Fang Y-Z. 1999. Effects of lu-duo-wei capsule on prolonging life span of housefly and Drosophila melanogaster. Am J Chin Med. 27:407-413.

[30] Wagner AE, Piegholdt S, Rabe D, Baenas N, Schloesser A, Eggersdorfer M, Stocker A and Rimbach G. 2015. Epigallocatechin gallate affects glucose metabolism and increases fitness and lifespan in Drosophila melanogaster. Oncotarget. 6(31):30568-30578.

[31] Niu Y, Na L, Feng R, Gong L, Zhao Y, Li Q, Li Y, and Sun C. 2013. The phytochemical, EGCG, extends lifespan by reducing liver and kidney function damage and improving age-associated inflammation and oxidative stress in healthy rats. Aging Cell. 12:1041-1049.

[32] Strong R, Miller RA, Astle CM, Baur JA, De Cabo R, Fernandez E, Guo W, Javors M, Kirkland JL, Nelson JF, Sinclair DA, Teter B, Williams D, Zaveri N, Nadon NL and Harrison DE. 2013. Evaluation of resveratrol, green tea extract, curcumin, oxaloacetic acid, and medium-chain triglyceride oil on life span of genetically heterogeneous mice. J Gerontol. 68(1):6-16.

[33] Baeza I, Castro NM De, Arranz L and De la Fuente M. 2010. Soybean and green tea polyphenols improve immune function and redox status in very old ovariectomized mice. Rejuvenation Res. 13(6):665-674.

[34] Aires D, Rockwell G, Wang T, Frontera J, Wick J, Tonkovic-capin M, Lu J, Lezi E, Zhu H and Swerdlow H. 2012. Potentiation of dietary restriction-induced lifespan extension by polyphenols. Biochim Biophys Acta. 1822(4):522-526.

[35] Kitani K, Yokozawa T and Osawa T. 2004. Interventions in aging and age-associated pathologies by means of nutritional approaches. Ann N Y Acad Sci. 1019:424-426.

[36] Lemon JA, Boreham DR and Rollo CD. 2005. A complex dietary supplement extends longevity of mice. J Gerontol. 60A(3):275-279.

[37] Kitani K, Osawa T and Yokozawa T. 2007. The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. Biogerontology. 8:567-573.

[38] Spindler SR, Mote PL, Flegal JM and Teter B. 2013. Influence on longevity of blueberry, cinnamon, green and black tea, pomegranate, sesame, curcumin, morin, pycnogenol, quercetin and taxifolin fed isocalorically to long-lived, F1 hybrid mice. Rejuvenation Res. 16(2):143-151.

[39] Archer CR, Köhler A, Pirk CWW, Oosthuizen V, Apostolides Z and Nicolson SW. 2014. Antioxidant supplementation can reduce the survival costs of excess amino acid intake in honeybees. J Insect Physiol. 71:78-86.

[40] Zhang B, Xiao R, Ronan EA, He Y, Hsu AL, Liu J and Xu XZS. 2015. Environmental temperature differentially modulates C. elegans longevity through a thermosensitive TRP channel. Cell Rep 11(9):1414-1424.

[41] Stiernagle T. 2006. Maintenance of C. elegans. WormBook. Feb 11:1-11.

[42] Win MTT, Yamamoto Y, Munesue S, Han D, Harada S-I and Yamamoto H. 2013. Validated liquid culture monitoring system for lifespan extension of Caenorhabditis elegans through genetic and dietary manipulations. Aging Dis. 4:178-185.

[43] Xiong LG, Chen YJ, Tong JW, Gong YS, Huang JA and Liu ZH. 2018. Epigallocatechin-3-gallate promotes healthy lifespan through mitohormesis during early-to-mid adulthood in Caenorhabditis elegans. Redox Biol. 14:305-