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Caenorhabditis elegans as an *in vivo* model for food bioactives: A review

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ABSTRACT

Caenorhabditis elegans (*C. elegans*) is being widely explored as an *in vivo* model to study the effects of food bioactives. These nematodes are largely advantageous over other *in vivo* models as they are relatively inexpensive, have a short generation time, and have a completely sequenced genome, among other advantages. *C. elegans* is a commonly used model to study diseases such as Alzheimer's and Parkinson's disease; however, researchers are finding they can also give insight into the health promoting effect of food-derived bioactive compounds. As consumers become more aware of the health benefits of the foods that they consume, the study of bioactive properties of foods and food constituents is becoming an important source of information. This review focuses on the advantages of using *C. elegans* as a model such as their short lifespans, high level of gene conservation relative to humans, and large number of progenies per reproductive cycle. They are also easily manipulated in order to perform controlled experiments on synchronous populations. Through review of recent literature, it is clear that *C. elegans* can be used to study a range of food derived compounds such as bioactive peptides, phenolic compounds, carbohydrates, and lipids. This review also provides information on potential challenges associated with working with this nematode. These challenges include the need for a sterile environment, potential inaccuracy when determining if the nematodes are dead, and the simplicity of the organism making it not suitable for all studies.

1. Introduction

Food derived bioactive compounds are a major source of interest among researchers and are proving to be the key to overall human health. Bioactive compounds are defined as compounds that are found in nature and positively effect human health. They have been found to be involved in mitigation of chronic disease such as obesity, diabetes, and dyslipidemia as well as exhibiting neuroprotection, among other health promoting effects (Biesalski et al., 2009; Teodoro, 2019). Originally, they were thought to be found only in plant sources; today, researchers are also finding bioactive compounds in non-plant sources such as fish, milk, and edible insects (Chen et al., 2020; Hall and Liceaga, 2020; Jayathilakan et al., 2018; Kanekanian, 2014). Previously, bioactive compounds were discovered and studied mostly *in vitro* and using some *in vivo* models with mice and rats. Although *in vitro* models are useful as preliminary studies to evaluate bioactive potential, *in vivo* studies are required to further prove the bioactive effects of food derived compounds. Unfortunately, many of the typically used *in vivo* models are costly, time consuming, and can have complicated genetics (Upadhyay and Palmberg, 2018; Xu et al., 2021). For this reason, researchers are looking at alternative *in vivo* models, such as *Caenorhabditis elegans*, to be a more practical model for studying the effects of food derived bioactive compounds *in vivo*.

2. Advantages of using *Caenorhabditis elegans* as an *in vivo* model

C. elegans are a free-living nematode (order: Rhabditida). They are an excellent research tool for many reasons including their simplicity, short life span, reproduction rate, as well as their conserved biological principles. *C. elegans* are approximately 0.25 mm upon hatching and grow to about 1 mm in length in adulthood. Due to their small size, hundreds can be hatched and developed on a single petri dish (Corsi et al., 2015). *C. elegans* have a translucent body making it easy to visualize the movement of fluorescently labeled proteins within them. This is especially important when studying the developmental processes of the nematode, or screening for mutations affecting function (Chalfie et al., 1994). Another characteristic of *C. elegans*, proving them to be a valuable research tool, is their short and rapid life cycle. Their embryogenesis takes only 16 h at 20 °C, and newly hatched *C. elegans* will reach adulthood in about 3 days. Before becoming an adult capable of

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reproducing, the nematodes cycle through four larvae life stages (L1, L2, L3, and L4) characterized primarily by an increase in size of the worm (Fig. 1). Upon hatching, L1 nematodes are typically about 0.25 mm in length. By L2, they grow to about 0.35 mm; they continue to grow to 0.50 mm in L3, followed by *ca.* 0.60 mm in L4, and finally reaching about 1.0 mm in adulthood stage (Altun and Hall, 2009). Once in adulthood, the nematodes begin producing and laying eggs for approximately 3 days. They live on a petri dish, feeding from *Escherichia coli* OP50 for several weeks before dying of senescence (Corsi et al., 2015). Their growth rate can be manipulated by temperature. For example, they grow best in the range between 12 °C and 25 °C, with the lower temperature producing slower growth rates. At temperatures above 25 °C they will stop reproducing and begin to perish. *C. elegans* are hermaphrodites meaning they can reproduce on their own by fertilizing themselves with stored sperm. One single nematode can produce about 300 progeny and populate an entire petri dish on its own (Corsi et al., 2015).

C. elegans populations are capable of being synchronized in order to conduct experiments with nematodes in the same life stage as seen in Fig. 2. To synchronize nematodes, they are first exposed to a hypochlorite solution (or 100% household bleach) for approximately 5 min. This solution will lyse the bodies of the nematodes but cannot permeate the eggs. Once all of the eggs have hatched, the nematodes are exposed to *E. coli* OP50, which serves as feed to the nematodes, and will begin to grow synchronously from stage L1 to L4 (Corsi et al., 2015). Most experiments begin when the nematodes reach the L4 stage, at around 40 h (at 20 °C) after hatching. In order to prevent the production of eggs, these L4 nematodes are exposed to a solution of 5′-fluorodeoxyuridine (FudR) to sterilize them (Wang et al., 2019). After this, the nematodes are ready to begin experimentation.

C. elegans were the first multicellular organism to have their genome completely sequenced. Through this process, it was found that they contain homologs for nearly 60–80% of human genes; this is extremely important for studying the effects of drugs and other compounds on human health (Aguilar-Toalá and Liceaga, 2021; Consortium, 1998; Kaletta and Hengartner, 2006). In this context, *C. elegans* have already proven to be valuable resources for studying diseases associated with aging or oxidative stress including Alzheimer's disease and diabetes (Forsythe et al., 2006; Luo, 2006). Oxidative stress resistance is reported to occur when the skinhead-1 (SKN-1) genes transcription factors are activated. In *C. elegans*, the skn-1 gene encodes a transcription factor that resembles mammalian nuclear factor erythroid 2–related factor 2 (Nrf2) and activates an antioxidant response (An and Blackwell, 2003; Tullet et al., 2017). Additionally, the *C. elegans* DAF-16 gene is found to be involved with the antioxidant defense system, stress response, and metabolism of the nematode (Murphy et al., 2003). Skn-1 and Daf-16 are both genes involved in the Insulin/IGF-1 (IIS) pathway, which is found to protect against oxidation. In addition to the IIS pathway, it was recently discovered that the epidermal growth factor (EGF) pathway is also involved in protection against oxidative stress in *C. elegans*. One important gene involved in this pathway is gst-4, which is often upregulated in order to provide an antioxidant response (Detienne et al., 2016; Tang et al., 2018). These as well as many other genes have direct homologous in humans and make this nematode valuable when determining the biological activity that certain bioactive compounds can offer to the human body.

It is estimated that *C. elegans* heredity only contributes about 20–50% of the lifespan of the nematode, with the remaining 50–80% likely due to the environment. Normally, *C. elegans* feeds on *E. coli*, however they can still intake nutrients from the medium in which they are grown whether *E. coli* is present or not (Johnson and Wood, 1982). These nutrients could include antioxidants or radical scavengers, which have been found to influence the aging pathways in *C. elegans* (Gill, 2006). Kim and colleagues found that platinum nanoparticles, which are a superoxide dismutase, displayed anti-aging properties in *C. elegans* (Kim et al., 2008). Additionally, other studies found that the lifespan of *C. elegans* increased when vitamin E was supplemented into their diet; this was attributed to slowing of development (Harrington and Harley, 1988). Obesity also has many links to lifespan as well. For example, when *C. elegans* were fed glaucarubinone, a phytochemical known to exhibit health promoting effects, their overall body fat decreased resulting in an increased lifespan (Zarse et al., 2011). An increased or decreased lifespan is often the result of other factors in the environment such as antioxidants or anti-obesity agents. These early studies as well as more recently conducted studies proved that *C. elegans* are a viable model to study bioactivities of compounds (Table 1).

There are several approaches that can be used to measure the bioactivity of food derived compounds in *C. elegans*. Fig. 3 outlines a proposed experimental design to measure the antioxidant activity of a bioactive compound (e.g., peptides); however, this basic approach can be adapted to study other bioactivities. Nematodes that had previously been exposed to a compound of interest can be subject to oxidation (e.g., acute and oxidative stress conditions) and their mean lifespan evaluated (e.g., after 24–48 h) in comparison to a control group. Lifespan is evaluated by counting alive (curved) and dead (straight) worms (Chen et al., 2020). Reactive oxygen species (ROS) can also be measured in nematodes who were previously exposed to a bioactive compound and an oxidant (e.g., Paraquat). In addition to lifespan and ROS analyses, *C. elegans* can be used to evaluate changes in gene expression in response to exposure to a compound of interest (Zhao et al., 2018).

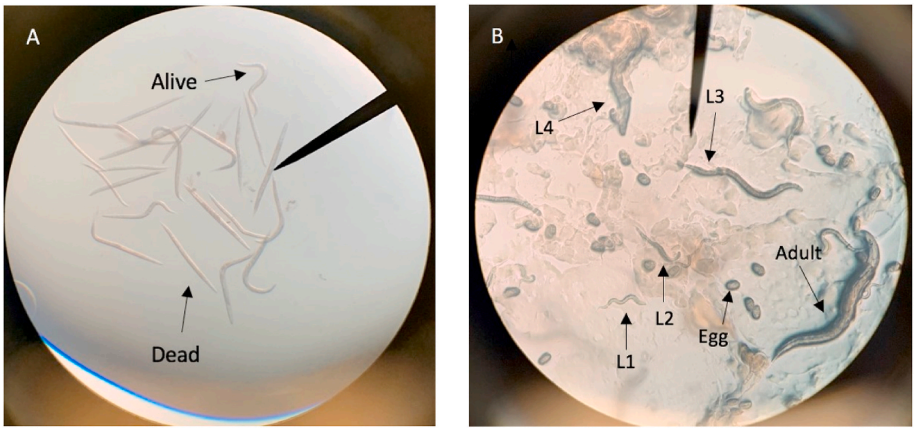

Fig. 1. **(A)** Representation of *C. elegans* physical appearance of live (curved) versus dead (straight or paralyzed) nematodes (40x magnification); **(B)** Size comparison of *C. elegans* at each stage of life, 100x magnification. L1-L4 indicate the four larvae growth stages from egg, larval 1 stage (L1) through larval 4 stage (L4), and finally the adult stage.

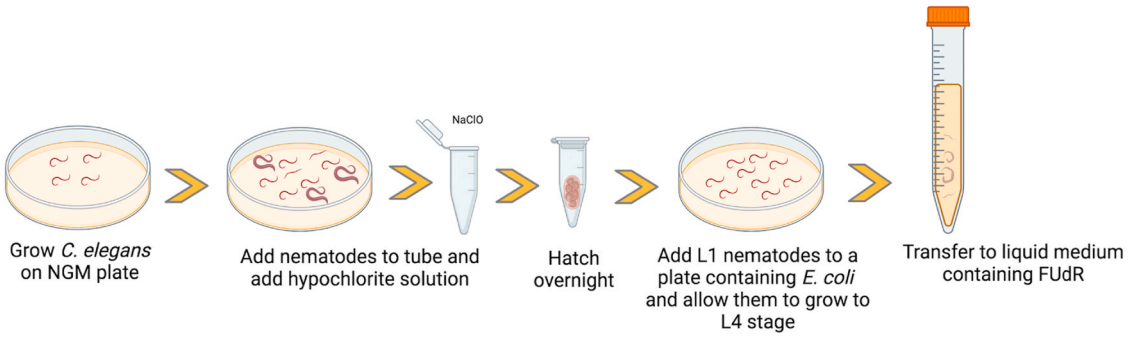

Fig. 2. Diagram of synchronization process for *C. elegans* of all stages of life (egg, larval 1 (L1) - larval 4 (L4), adult) grown on petri dishes containing nematode growth media (NGM). These nematodes are then collected and mixed with a hypochlorite solution to lyse the nematode bodies and release the eggs inside the adult nematodes. These eggs hatch in about 8 h and are arrested in the L1 stage until exposed to *E. coli* OP50 (their food source), which allows for experiments to be conducted with nematodes of the same stage of life. These L1 nematodes grow to L4 in about 42–46 h and should then be exposed to 5′-fluorodeoxyuridine (FUdR) to inhibit reproduction, before conducting experiments. *Figure created with BioRender.com*.

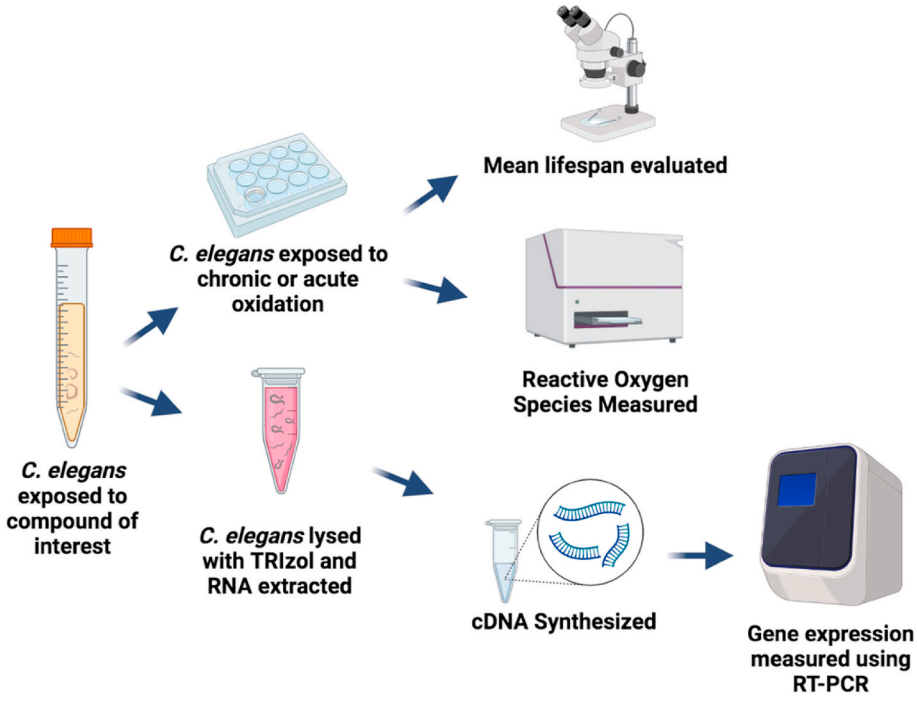

Fig. 3. Experimental design using *C. elegans* to evaluate the antioxidant properties of food derived bioactive peptides. *C. elegans* that were previously exposed to a compound of interest (e.g., bioactive peptides) can be exposed to an oxidant. *C. elegans* mean lifespan can be evaluated by counting the number of live and dead worms over time and reactive oxygen species can also be measured. In addition, gene expression can be measured by lysing *C. elegans* previously exposed to the compound of interest. RNA can be isolated from the lysed nematodes and cDNA can be synthesized. This cDNA can then be used to measure gene expression via RT-PCR. *Figure created with Biorender.com.*

3. Application of *C. elegans* to study bioactive peptides

Bioactive peptides have been identified within food proteins and are showing potential effects on the reduction of hypertension, inflammation, type-2 diabetes, microbial infections, immune disorders, and oxidation, among others (Beermann and Hartung, 2013; Udenigwe and Aluko, 2012). Bioactive peptides are hidden within the primary structure or amino acid sequence of proteins and are inactive when the entire protein is intact; however, upon cleavage of certain peptide bonds, or proteolysis, certain peptides with biological activities can be released and become active (Udenigwe, 2014). Proteolysis can occur during gastrointestinal digestion or by using exogenous, commercial proteases (Beermann and Hartung, 2013; Li-Chan, 2015). Bioactive peptides can also be generated through fermentation by microbial enzymes (Beermann and Hartung, 2013; Yamamoto, 1997). Most bioactive peptides share a common structure of about 2–20 amino acids in length with a large percentage of those being hydrophobic residues. Additionally, they have been found to contain high levels of proline, lysine or arginine (Kitts and Weiler, 2003). Through extensive research into bioactive peptides, they have shown to affect the digestive, endocrine, cardiovascular, immune, and nervous systems (Boelsma and Kloek, 2009; Gilani et al., 2008; Sánchez and Vázquez, 2017).

One of the most widely studied bioactivities of food peptides, modeled in *C. elegans*, is the antioxidant effect (Table 1). Researchers have found that oxidative stress resistance occurs when the SKN-1, a transcription factor involved in the IIS pathway, is activated. The ortholog of this gene, in humans, is the NRF2, a well-known antioxidant gene (An and Blackwell, 2003; He and Ma, 2009). Additionally, the *C. elegan* DAF-16 gene, also involved in the IIS pathway, is found to be involved with the antioxidant defense system, stress response, and metabolism of the nematode (Murphy et al., 2003). Several food-derived peptides have proven to possess antioxidant capacities when supplemented into *C. elegans* diet. For example, the antioxidant capacities of peptides from several edible marine species have shown resistance to oxidative stress in *C. elegans*. These include the saltwater clam (*Meretrix meretrix),* purple sea urchin (*Strongylocentrotus nudus*), mussel (*Mytilus edulis)*, and sea cucumber (*Apostichopus japonicus*). These peptides increased the lifespan of *C. elegans* when exposed to an oxidant (Jia

Table 1
Recent publications using *C. elegans* as a model for studying bioactive compounds.

Bioactive Compound	Source	Bioactivities Studied	*C. elegans* strain used	Evaluation used	Reference
Carbohydrates	Barley β-glucan	Anti-obesity	N2	Lifespan; Oil red staining; Triglyceride assay; RT-PCR; SCFA assay;	Xiao et al. (2020)
	Betaxanthins	Antioxidant	N2; TJ375	Lifespan; Quantification of *hsp-16.2::GFP*	Guerrero-Rubio et al. (2021)
	Bitter Melon (Momordica charantia)	Anti-obesity	N2; mu86; e1370; nr2014; tm420; tm331; wa36	Lifespan; Oil red staining; Triglyceride level; RT-PCR	Zhu et al. (2021)
	Casein-maltodextrin Maillard Conjugates	Antioxidant; anti-aging	N2	Lifespan; Thermal stress; Lipofuscin level; SOD and CAT activity	Sun et al. (2021)
	Fructan exopolysaccharides	Antioxidant	N2; TJ356	Survival under oxidative stress; Lifespan; Daf-16 localization;	Lakra et al. (2021)
	Fucoidan from algae (*Fucus vesiculosus, Undaria pinnatifida, Macrocystis pyrifera)*	Antimicrobial	N2	Bacterial Quantification	Palacios-Gorba et al. (2020)
	Resistant starch; Fermented starch; Short chain fatty acids	Anti-obesity	N2	Red Niles staining	Zheng et al. (2010)
	Straw mushroom (*Volvariella volvacea*)	Anti-obesity	N2; ok524; mu86; nr2041; tm420; tm331; wa36; tm3116	Locomotive behavior; worm size; growth rate; reproductive assay; Oil red staining; Triglyceride quantification; RT-PCR; Detection of GFP-labeled proteins	Bai et al. (2021)
	Wheel wingnut (*Cyclocarya paliurus*)	Anti-obesity	N2; XA7702; RB1716; CE541; CE548; BX107; BX106; BX153; BX160; BX110; WBM170; ZXW618	Triglyceride quantification; Oil red staining; Lipid droplet analysis; Pharyngeal pumping assays; Body size assay; RT-PCR; Visualization of *SBP-1::GFP* and *ACS-2::GFP*	Lin et al. (2020)
Lipids	Borage seed (*Borago officinalis*) oil	Anti-obesity	N2	Red nile staining;	Navarro-Herrera et al. (2018)
	Conjugated linoleic acid	Anti-obesity	N2; CF1553; ok524; ok343; tm498; e1259; q339	Lifespan under oxidative stress; ROS quantification; Quantification of reporter genes; RT-PCR; Triglyceride quantification; Worm size/locomotion;	(Sangha et al., 2013; Shen et al., 2018)
	Deuterated polyunsaturated fatty acids	Antioxidant	N2; bx24; tk22; cl2166; cf1553	Lifespan; Lipid analysis; TBARS Assay; Lipid peroxidation assay; Fluroescent microscopy of gst-4 and sod-3; egg counting assay	Beaudoin-Chabot et al. (2019)
	Dihomo-gamma-linolenic acid	Anti-obesity	N2; wa9*;* wa22; wa7*;* wa14*;* wa9; hj13; ok693	Nile red staining; Oil red staining; Lipid extraction; Pharyngeal pumping; sterility; RT-PCR	Navarro-Herrera et al. (2018)
	Lipophilic Ingredients	Anti-obesity;	N2	Fatty acid composition; Oil red staining; Worm size; Food intake; SOD, GSH-PX and CAT activity; MDA content; Tryglyceride quantification	Guo et al. (2021)
	Phytoecdysteroid enriched quinoa seed (*Chenopodium quinoa*)	Antioxidant; Anti-aging	N2	ROS quantification; fat accumulation	Graf et al. (2017)
	Plant sterol; galactooligosaccharides	Antioxidant	N2; GR1307; CB1370	Oxidative stress survival assay; lifespan assay;	López-García et al. (2020)
	Red algae (*Chondrus crispus*)	Antioxidant	N2	Oxidative stress survival assay; ROS quantification; RT-PCR	Sangha et al. (2013)
Protein/ Peptides	*Arca subcrenata*	Anti-obesity; Antioxidant	N2	Lifespan; Pharyngeal pumping; Nile red staining; ROS quantification; Lipofuscin assay; Oxidative stress survival assay; RT-PCR	Shi et al. (2021)
	Cocoa (*Theobroma cacao*) peptides	Antioxidant; Neuroprotective	N2; CL4176; GR1321	Oxidative stress survival assay; Paralysis assay; $A\beta_{42}$ aggregation assay; Rile red staining; RT-PCR	Martorell et al. (2013)
	Female ginseng (*Angelica sinensis*)	Antioxidant	N2	Oxidative stress survival assay; ROS quantification; MDA content; Age pigment accumulation; Pharyngeal pumping;	Wang et al. (2016)
	Golden Cuttlefish (*Sepia esculenta*)	Anti-obesity; Antioxidant	N2; CF1553	Oxidative stress survival assay; SOD activity; ROS and MDA quantification; sod-3p::GFP expression; RT-PCR; Oil red staining;	Yu et al. (2020)
	Lactoferrin	Antioxidant; Neuroprotective	N2; CL4176	Paralysis assay; Oxidative stress survival assay; Lifespan assay; Microarray analysis	Martorell et al. (2017)
	Maize	Neuroprotective	N2; GMC101	Aβ-induced paralysis; ROS quantification; β-amyloid quantification;	Zhang et al. (2016)
	Mussel (*Mytilus edulis*)	Antioxidant	N2	Lifespan analysis; Locomotion quantification; Oxidative stress analysis; Body length quantification; Lipofuscin content; ROS quantification; RT-PCR	Zhou et al. (2018)
	Purple Sea Urchin (*Strongylocentrotus nudus*)	Antioxidant	N2; GR1352; LG345; CL2070	Oxidative stress survival assay; ROS quantification; SOD-2 and HSP-16.2	Zhao et al. (2018)

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Table 1 (*continued*)

Bioactive Compound	Source	Bioactivities Studied	*C. elegans* strain used	Evaluation used	Reference
				expression level; Nuclear localization DAF-16 and SKN-1; RT-PCR	
	Round Scad (*Decapterus maruadsi*)	Antioxidant	N2	Lifespan assay; ROS quantification; SOD and CAT activity; Oxidative stress survival assay;	Chen et al. (2020)
	Saltwater Clam (*Meretrix meretrix*)	Antioxidant	N2; GR1352; CF1553	Oxidative stress survival assay; Nuclear localiation of Daf-16; SOD-2 expression levels; RT-PCR; RNAi interference	Jia et al. (2018)
	Sea Cucumber (*Apostichopus japonicus*)	Anti-aging; antioxidant	N2	Oxidative stress survival assay; ROS quantification; SOD and CAT activity; Age pigment accumulation; Lifespan; Food clearance; Body length quantification	Guo et al. (2020)
	Sea Cucumber (*Apostichopus japonicus*)	Antioxidant	N2	Oxidative stress survival assay	Lu et al. (2021)
	Sesame Cake (*Sesamum indicum* L.)	Antioxidant	TK22; PS3551; EU1; DA465	Lifespan assay; Pharyngeal pumping; Food intake; Lipofuscin accumulation; Oxidative stress survival assay; ROS quantification; Antioxidant enzyme assay; RT-PCR; Transcription factor translocation;	Wang et al. (2016)
	Sesame Cakes (*Sesamum indicum* L.)	Antioxidant; Neuroprotective	N2	Aβ-induced toxicity; Oxidative stress survival assay; Lifespan analysis; Locomotion; Paralysis; ROS quantification; Aβ deposition; RT-PCR	Ma et al. (2017)
	Soybean Protein Isolate	Antioxidant	N2; CF1553	Oxidative stress survival assay; ROS quantification;	Ma et al. (2016)
	Stripped weakfish (*Cynoscion guatucupa*)	Antioxidant	N2	Oxidative stress survival assay	Lima et al. (2021)
Phenolic Compounds	African marigold (*Tagetes erecta* L.)	Neuroprotective	N2; CL4176	Toxicity; Oxidative stress survival assay; Lifespan assay; Paralysis assay	Moliner et al. (2018)
	Amla (*Phyllanthus emblica*)	Neuroprotective	CL4176	Anti-neurotoxicity assay	Rose et al. (2018)
	Ascomycetes (*Cordyceps sobolifera*)	Antioxidant	N2; XA7702; RB1716; CE541; CE548; BX107; BX106; BX153; BX160; BX110	Tryglyceride content; Oil red staining; Lipid droplet accumulation; Pharyngeal pumping; Body size; RT-PCR; Visualization of *SBP-1::GFP* and *ACS-2::GFP*	Lin et al. (2018)
	Baru Pulp (*Dipteryx alata*)	Antioxidant	N2; CF1553; CL2166; TJ356	Toxicity; Progeny quantification; Heat and Oxidative stress survival assays; Lifespan; SOD-3, Daf-16 and GST-4 expression;	Leite et al. (2020)
	Blackberry cultivar: BRS Xungu	Antioxidant	N2	ROS quantification	Moraes et al. (2020)
	Butía (*Butia catarinensis* and *Butia eriospatha*) and Arumbeva (*Opuntia elata*)	Antioxidant	N2; TJ356	Oxidative stress survival assay; ROS quantification	Rockett et al. (2020)
	Butía (*Butia eriospatha*)	Antioxidant	N2; CF1553; GA800	Oxidative stress survival assay; Lifespan assay; SOD and CTL expression; ROS quantification;	Tambara et al. (2020)
	Cabuçu (*Coccoloba alnifolia*)	Antioxidant	N2	Toxicity; Oxidative stress survival assay;	Melo et al. (2020)
	Caffeic and Dihydrocaffeic Acids	Antioxidant	N2	Oxidative stress survival assay; ROS quantification; Lifespan assay; RT-PCR	Gutierrez-Zetina et al. (2021)
	Cashew Leaf (*Anacardium occidentale* L.)	Antioxidant	N2; TK22; TJ375; CF1553; TJ356; CF1038; BA17; EU1; CL2166	Oxidative stress survival assay; ROS quantification; Quantification of HSP-16.2::GFP, GST-4::GFP, and SOD-3::GFP; Localization of Daf-16 and SKN-1; Brood size; Body length; Lipofuscin quantification; Pharyngeal pumping; Lifespan analysis	Duangjan et al. (2019)
	Guarana (*Paullinia cupana*)	Antioxidant; Neuroprotective	N2; CL4176; dvls27; CL2006; AM141; HA759; TJ375; CF1553; CL2166	Aβ- protection; RNAi interference; Neuronal survival assay; Oxidative stress survival assay; ROS quantification; reporter gene analysis;	Boasquívis et al. (2018)
	Nonencapsulated phenolic compounds	Antioxidant	N2	Lifespan; Oxidative stress survival assay;	Davila-Trujillo et al. (2021)
	Olive Leaves (Olea europare L)	Antioxidant	N2; TJ375; TJ356	Food clearance assay; Fertility assay; Thermal stress assay; ROS quantification; Visualization of the HSP-16.2::GFP; MDA levels; Nuclear localization of DAF-16;	Luo et al. (2019)
	Orange	Antioxidant	N2	Lifespan assay; Motility assay; Reproduction assay; Age-pigment assay; Thermo and UV stress resistance; ROS quantification; MDA levels; RT-PCR	Wang et al. (2020)
	Peony (*Paeonia suffruticosa*)	Antioxidant	N2	Oxidative stress survival assay	Wang et al. (2020)
	Phenolic Compounds	Anti-obesity	N2	Nile Red staining; Oil Red staining; DHE staining; Lifespan analysis; Worm size; RT-PCR	Aranaz et al. (2020)
	Pterodon emarginatusin	Antioxidant; Anti-obesity	N2	Lifespan assay; Brood size assay; ROS quantification; Oxidative stress survival	Dal Forno et al. (2019)

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Table 1 (*continued*)

Bioactive Compound	Source	Bioactivities Studied	*C. elegans* strain used	Evaluation used	Reference
				assay; SOD and CAT activity; Lipid and triglyceride levels	
	Purple Pitanga Fruit (*Eugenia uniflora* L.)	Antioxidant	N2; CF1553; GA800; CL2070; TK22; CF1038	Oxidative stress survival assay; Reproductive assay; Lifespan assay; ROS quantification; SOD-3 and HSP-16.2 expression;	Tambara et al. (2018)
	Raspberry (*Rubus idaeus* L.)	Antioxidant	N2; e1370; TJ356	Lifespan assay; Motility assay; Lipofuscin assay; Heat shock assay; Nuclear localization	Song et al. (2020)
	Red Cabbage (*Brassica oleracea* L. var. capitata L. f. rubra)	Antioxidant	N2; GR1307; VC199; MT2605	Lifespan assay; Oxidative stress survival assay; ROS quantification; Body length assay; RT-PCR	Zhang et al. (2021)
	Red mold (*Monascus*) dioscorea	Antioxidant	N2; GR1307; CF1038; TK22; CF1553; TJ356	Oxidative stress survival assay; ROS quantification; DAF-16 localization; RT-PCR	Shi et al. (2012)
	Rosemary Flowers (*Rosmarinus officinalis* L.)	Antioxidant	N2; SS104	Acute toxicity; Oxidative stress survival assay; Lifespan assay;	Moliner et al. (2020)
	Rugosa Rose (*Rosa rugosa*) tea	Anti-aging	N2	Lifespan assay; Thermotolerance assay; Oxidative stress survival assay;	Zhang et al. (2019)
	Strawberry (*Fragaria* × *ananassa* cv. Romina)	Antioxidant; Neuroprotective	N2; CL4176; CL802; TJ375; TJ356; LD1; CF1553	Pharyngeal pumping; Reproductive rate; Lifespan assay; ROS quantification; Paralysis assay; Beta amyloid analysis; Daf-16, SKN-1, HSP-16.2, SOD-3 quantification;	Navarro-Hortal et al. (2022)
	Umbrella Cheese Tree (*Glochidion zeylanicum*)	Antioxidant	N2; TK-22 (mev-1[kn1]III), TJ375 (gpIs1[hsp-16.2::GFP]), CF1553 (muls84 [pAD76(sod-3::GFP)]), TJ356; CF1038; BA17; EU1; CL2166; LD1	Oxidative stress survival assay; ROS quantification; HSP-16.2, GST-4; SOD-3 expression; DAF-16 and SKN-1 localization; Pharyngeal pumping; Lifespan assay; Brood size;	Duangjan et al. (2019)
	Walnut Kernel (*Diaphragma juglandis fructus*)	Antioxidant	N2	Lifespan assay; Lipofuscin accumulation; Oxidative stress survival assay; ROS quantification; MDA analysis;	Hong et al. (2021)
	Zalema Grape	Antioxidant	N2	Oxidative stress survival assay; ROS quantification	Jara-Palacios et al. (2013)

et al., 2018; Lu et al., 2021; Zhao et al., 2018; Zhou et al., 2018). In addition to marine species with antioxidant capacities, recent studies have also discovered these antioxidant properties in many plant species. For example, Ma et al. (2016) reported that protein isolates from soybean increased the survival of *C. elegans* exposed to an oxidant (i.e., juglone) by 24%. In addition, the exposure of these nematodes to soybean peptides isolates also decreased ROS levels while upregulating a gene known to be involved in antioxidant pathways such as superoxide dismutase 3 (SOD-3) (Ma et al., 2016). In other studies, sesame cakes, a by-product of sesame oil production, showed similar antioxidant capacities with a reduction of ROS levels and an upregulation of antioxidant gene expression (Z. Wang et al., 2016), while stripped weakfish (*Cynoscion guatucupa*) peptides were reported to increase the antioxidant capacities in *C. elegans* (Lima et al., 2021). These studies demonstrate how the use of *C. elegans* is becoming a valuable and reliable way to study the protection imparted by food derived peptides against oxidation.

In addition to the investigation of antioxidant effects of peptides in *C. elegans*, researchers are also using this nematode to determine the anti-obesity capacities of food derived peptides. In *C. elegans*, the inactivation of 305 genes leads to decreased body fat while the activation of 112 genes leads to increased body fat (Ashrafi, 2007). Many of these pathways are conserved between humans and *C. elegans* (Jones and Ashrafi, 2009). In this context, fat mobilization in *C. elegans* is dependent on certain lipases that have orthologs in humans and are responsible for the liberation of stored triglycerides in fat droplets (Wang et al., 2008). Fat accumulation can also be visualized using lipid affinity dyes which make for easier quantification of fat deposits in *C. elegans* (Li et al., 2005). Nomura and colleagues found that adipogenesis and lipogenesis involves the sterol-binding proteins that also participate in lipid synthesis in humans. This process is conducted in *C. elegans* by sbp-1, which has a homolog in humans, sterol regulatory element-binding protein 1 (SREBP-1) (Nomura et al., 2010). The high level of fat metabolism pathway conservations between *C. elegans* and humans makes them an excellent organism to study the effects food derived peptides on obesity. A recent study by Yu et al. (2020) showed that a novel peptide (1159 Da) from golden cuttlefish (*Sepia esculenta*) supplemented into the high-fat diet of *C. elegans*, resulted in significantly ($p < 0.05$) decreased fat accumulation. This was measured using an oil red staining technique that allowed for the visualization and quantification of lipid droplets, the major fat storing organelle in the bodies of nematodes (Yu et al., 2020; Zhang et al., 2010). Another technique used to visualize and quantify fat accumulation in *C. elegans*, is the Nile red lipophilic dye. This technique was used to determine the anti-obesity properties of two novel peptides from *Arca subcrenata* Lischke (a mollusk used in Chinese traditional medicine), which decreased fat accumulation in the nematodes by nearly 17% compared to the control (Shi et al., 2021). Although few studies have been conducted in *C. elegans* to determine the anti-obesity capacities of food derived peptides; they showed that *C. elegans* can be a powerful model for the *in vivo* examination of food derived peptides towards controlling obesity.

The β-Amyloid peptide accumulation is a critical contributor involved in the progression of Alzheimer's disease. It contains 39 to 42 amino acids and is derived from the β-amyloid precursor protein. These proteins accumulate in the brain, form plaques, and lead to dementia and deterioration of the brain (Link, 1995). Several transgenic strains of *C. elegans* (e.g., GMC101 and CL4176) have been created to carry the gene for β-amyloid peptides and model the bioactive peptides' ability to protect against β-amyloid peptide toxicity and Alzheimer's disease (Ma et al., 2017; Martorell et al., 2013). For instance, hydrolyzed cocoa (the unprocessed bean from *Theobroma cacao*) peptides were supplemented into the diet of *C. elegans*-CL4176 and β-amyloid peptide concentrations were quantified via immunoblotting. The supplementation of cocoa peptides (1 μg/mL) into the transgenic nematodes diet caused a 50%

decrease in β-amyloid deposits (Martorell et al., 2013). Similarly, when sesame cake peptides were supplemented into the diet of transgenic nematodes, a significant reduction in β-amyloid accumulation and thus reduced risk of Alzheimer's disease was evaluated (Ma et al., 2017). In another study, transgenic *C. elegans* fed a maize tetrapeptide (10 mM) had 19.5% less β-amyloid aggregation. In addition, when these nematodes underwent oxidative stress, the maize peptides were still able to reduce β-amyloid toxicity (Zhang et al., 2016). The use of transgenic strains of *C. elegans* proves to be a viable model to study the protection from β-amyloid toxicity using food derived peptides.

4. Application of *C. elegans* to study bioactive phenolic compounds

Phenolics are recognized as one of the most prominent sources of bioactive compounds. They are most abundantly found in plant sources, are secondary metabolites within plants, and are characterized by the presence of one or more aromatic rings in their structure with at least one hydroxyl group attached (Nino et al., 2021). After cellulose, phenolic compounds are the most abundant category of compounds found in plants. There are many phenolic compounds with different structures, each serving a function within the plant. They are known to be involved in structural support, protection from ultraviolet (UV) radiation, defense against herbivores, inhibition of growth to nearby plants, and many more critical functions within the plant system (Laura et al., 2019; Nino et al., 2021). The structures of phenolic compounds lead to their function not only in plants but also within the human body, once they are consumed. For example, they have been found to be involved in inhibition of enzymes, modification of genes, protein phosphorylation, as well as other cellular regulations (Minatel et al., 2017). The most widely recognized bioactive property attributed to phenolic compounds is related to their antioxidant capacities. The structure of a specific compound relates to its ability to quench free radicals. To study free radical quenching *in vitro*, DPPH (2-diphenyl-1-picrylhydrazyl radical cation) and ABTS (2,20 -azinobis (3-ethylbenzothiazoline-6-sulphonic acid) radical assays are often used (Nino et al., 2021). These activities can relate to varying degrees of hydroxyl groups or different substitutes on the aromatic ring. As previously mentioned, it has also been found that these compounds are able to modulate gene and enzyme function which can leave to increased resistance to oxidation (Minatel et al., 2017).

The antioxidant effects of many foods containing high levels of phenolic compounds are being studied using *C. elegans* as an *in vivo* model. In one study, red cabbage juice (rich in total phenolics, ascorbic acid, glucosinolates, and anthocyanins), increased nematode survival under oxidative stress by 171%, while green cabbage showed no significant effect on nematode survival. This difference in oxidative resistance is attributed to red cabbages' significantly higher phenolic content compared to green cabbage, mainly caffeic, *p*-coumaric, ferulic, and sinapic acids (N. Zhang et al., 2021). Similarly, raspberry extracts, high in phenolic compounds, supplemented into the diet of *C. elegans* at a concentration of 80 mg/mL increased the mean lifespan of the nematodes by 29.7%. It was also found that raspberry extracts relative expression of sod-3 and ctl-2, two genes involved in nematode oxidation resistance, upregulated 2.20 and 1.93-fold, respectively. The phenolic compounds present in the raspberry extract likely caused this gene regulation leading to increased resistance to oxidation in *C. elegans* (Song et al., 2020). Moraes et al. (2020) reported a new blackberry cultivar (BRS Xingu) containing a multitude of phenolic compounds including, 5 anthocyanins, 5 phenolic acids, and 5 non-anthocyanin flavonoids that was tested for antioxidant activity in *C. elegans*. It was found that BRS Xingu decreased ROS levels in the nematodes by 30.6% after juglone exposure (Moraes et al., 2020). In another study, nanoencapsulated phenolic compounds from wine residues were also tested for *in vivo* antioxidant properties. Researchers found that the wine residue phenols displayed antioxidant capacities, showing lower ROS levels and increased longevity in *C. elegans*. These results suggest that the nanoencapsulation of phenolic compounds could prove useful in preserving and delivering these bioactive compounds through food products (Davila-Trujillo et al., 2021). These studies emphasize the importance and applicability of *C. elegans* as models to determine the antioxidant capacities of food derived phenolic compounds.

The use of *C. elegans* to study the anti-obesity properties of phenolic compounds in foods has also been reported. Wang et al. (2014) found that on a cellular level, certain phenolic compounds are able to suppress adipose differentiation and triglyceride accumulation as well as increase the instance of lipolysis or the breakdown of triglycerides into glycerol and free fatty acids. Additionally, phenolic compounds are able to modulate signaling pathways involved in adipogenesis (Wang et al., 2014). *C. elegans* have only been used a couple of times to study the anti-obesity capacities of phenolics. When *C. elegans* were exposed to the fruit oil extract (1 mg/mL) of *Pterodon emarginatus*, a decrease in lipid droplets occurred. In addition, with an increase in extract concentration, there was a decrease in triglyceride levels in the nematodes which was attributed to the overall high phenolic content, 1158.96 ± 56.01 mg GAE/mL oil (Dal Forno et al., 2019). In a second study, the anti-obesity effects of several isolated phenolic compounds were evaluated. From this study, it was concluded that of the different phenolic compounds evaluated, resveratrol had the strongest anti-obesity activity with a 31% reduction in mean fat content. Resveratrol was able to decrease lipid accumulation as well as increase the lifespan of *C. elegans*. In addition to resveratrol, other phenolic compounds exhibited similar effects. For example, apigenin caused an activation of the lipid mobilization response in nematodes while vanillic acid caused protein structural changes, both considered lipid-lowering effects (Aranaz et al., 2020). These two studies have provided valuable insight into the anti-obesity capacities of food derived phenolic compounds *in vivo*.

Like bioactive peptides, phenolic compounds are also reported to be involved in decreasing β-amyloid protein toxicity and thus the prevention of Alzheimer's disease. Certain phenolic acids are found to reduce the oligomerization of β-amyloid and reduce the synaptic dysfunction caused by these oligomers (Ono et al., 2012). Studies have found that methanol extracts of strawberries, containing high levels of the phenolic compounds (i.e., ellagic acid and pelargonidin-3-glucoside), exhibit these neuroprotective effects in *C. elegans*. For example, when transgenic *C. elegans* (CL4176) were exposed to these strawberry methanol extracts, paralysis in the nematodes was significantly ($p < 0.05$) delayed. This was attributed to the extracts' ability to reduce β-amyloid aggregations in the nematodes (Navarro-Hortal et al., 2022). Similarly, extracts from Mexican marigold (*Tagetes erecta* L.), an edible flower containing the polyphenols laricitin and glycosides, was able to delay the PT_{50} (time when 50% of nematodes were paralyzed or dead) by 33% in the transgenic strain CL4176 (Moliner et al., 2018). These studies emphasize the importance and applicability of *C. elegans* as models to determine the *in vivo* antioxidant, anti-obesity and anti-neurotoxicity effects of phenolic compounds (Table 1).

5. Application of *C. elegans* to study bioactive carbohydrates

Many oligosaccharides and polysaccharides have been found to improve human health in many ways. Dietary fibers are one of the main categories of carbohydrates known to positively influence human health. Dietary fibers are indigestible carbohydrates that travel through the human digestive system relatively untouched until they reach the colon. In the colon, a host of microorganisms feed on these undigested carbohydrates. The content of these microorganisms heavily influences overall wellness of the human body and the consumption of dietary fiber promotes a healthy microbiota (Deehan and Walter, 2016). The consumption of functional carbohydrates like fiber have been known to be involved in a lower risk of chronic diseases including heart disease, hypertension, diabetes, and certain types of cancer (Anderson et al., 2009). Recently, the bioactive effects of food derived carbohydrates

have been studied using *C. elegans* as a model (Table 1).

One of the most well-known bioactive properties of carbohydrates is their ability to play a role in decreasing obesity. It has been reported numerous times that dietary fiber intake increases the feeling of satiety, thus decreasing food consumption (Howarth et al., 2001; Sarker and Rahman, 2017). In addition, the fermentation of undigestible carbohydrates in the colon has been linked to the production of short-chain fatty acids. These short chain fatty acids have been found to prevent fat accumulation and insulin resistance (McNabney and Henagan, 2017). In *C. elegans*, similar obesity inhibiting effects from food derived carbohydrates are being evaluated. For instance, Zhu and colleagues used *C. elegans* to study water and alkali soluble polysaccharides from bitter melon. Both polysaccharide types were found to decrease fat accumulation in nematodes, with the alkali-soluble polysaccharides having a greater inhibitory effect toward triglycerides. In this same study, three genes (*fat-5*, *fat-6* and *fat-7*) were found to be involved in this lipid lowering effect of these polysaccharides (Zhu et al., 2021). Similarly, raw barely and fermented barley β-glucans were found to decrease the incidence of obesity in *C. elegans* by decreasing triglyceride accumulation in the nematodes. However, the fermentation of this β-glucan significantly ($p < 0.05$) improved its inhibitory fat accumulation effect. Further assessment of the fermented barley β-glucan determined that its upregulation of nuclear hormone receptor 49 (nhr-49), enoyl-CoA hydratase (ech-1), carnitine palmitoyl transferase-1 (cpt-1), and carnitine palmitoyl transferase-2 (cpt-2) in nematodes likely contributed to the observed anti-obesity effect (Xiao et al., 2020). Similarly, polysaccharides from a tropical species of edible mushroom *Volvariella volvacea,* reduced triglyceride levels by 24% in *C. elegans* and decreased the accumulation of fat through the aak-2/nhr-49-mediated fatty acid synthesis pathway (Bai et al., 2021). It is known that *C. elegans* contain a mediator-15 gene (mdt-15), which is involved in the fatty acid metabolism pathway, and it has a homolog in humans, arc105 (Yang et al., 2006). When *Cyclocarya paliurus,* a species of wingnut tree leaves commonly used for tea in China, were supplemented into the diet of *C. elegans*, the mdt-15 gene was modulated, causing a 52% decrease in fat accumulation compared to control nematodes. This suggests that the mdt-15 homolog (arc105) is likely involved in the anti-obesity effects mediated by *C. paliurus* leaves (Lin et al., 2020). These studies demonstrate that *C. elegans* is a useful model to study the anti-obesity effects of food derived carbohydrates *in vivo* and their results likely correlate with the effects that these carbohydrates have in the human body upon consumption.

Carbohydrates are also known to be involved in antioxidant activities both *in vitro* and *in vivo*. It is found that many known antioxidant compounds such as vitamin C travel through the small intestine attached to dietary fibers. Once these dietary fiber and antioxidant compounds reach the colon, they release from one another (Arranz et al., 2010; Vitaglione et al., 2008). Although this occurs with many dietary fibers, not all carbohydrates possess this mechanism. In *C. elegans*, the antioxidant properties of galactooligosaccharide-enriched beverages were evaluated. Results showed that when this enriched beverage was supplemented into the diet of nematodes under acute oxidative stress, their survival rate was increased by 12–16%, compared to the control. Similarly, when these nematodes were exposed to chronic oxidative stress, their survival was increased by 17–26% (López-García et al., 2020). The antioxidant properties of fructan exopolysaccharide produced by *Weissella cibaria* MD2, a gram-positive bacterium, were analyzed in order to determine their use in food systems. Under juglone oxidative stress, nematodes exposed to 100 μg/mL fructan exopolysaccharide lived 64% longer than the control nematodes not exposed to the carbohydrate. Through this study, it was also found that these fructan exopolysaccharide are able to activate the daf-16 pathway, the known antioxidant defense pathway (Lakra et al., 2021). *C. elegans* were also used to determine if a protein-carbohydrate conjugate, casein-maltodextrin, could be used to encapsulate proanthocyanin and propagate its antioxidant properties in nutraceuticals. Nematodes exposed to this conjugate lived on average 5 days as opposed to the control (3 days). An increase in superoxide dismutase (SOD) and catalase (CAT) activity was also increased, further proving its antioxidant activity. From this study it was discovered that the casein-maltodextrin conjugate did preserve the antioxidant properties of the proanthocyanin and in fact enhanced their protective effect (Sun et al., 2021).

Recently, researchers have begun looking into the antimicrobial properties of certain natural and synthetic carbohydrates. With the increase in microbial antibiotic resistance, new antimicrobial sources are necessary. One study used fucoidan, a long chain sulfated polysaccharide from kelp (*Undaria pinnatifida)*, to determine its antimicrobial properties. When *C. elegans* were exposed to an environment containing *Helicobacter pylori* and fucoidan, there was a much lower concentration of *H. pylori* in the nematodes' digestive tract compared to the control (nematodes not exposed to fucoidan), which allowed the nematodes to live longer (Palacios-Gorba et al., 2020). This study is the first indication that *C. elegans* can also be a model for evaluating the antimicrobial activity of carbohydrates. Carbohydrates, whether on their own or in conjunction with other antioxidant compounds, have proven to exhibit antioxidant, anti-obesity, and antimicrobial activity in *C. elegans* models.

6. Application of *C. elegans* to study bioactive lipids

Certain lipids are capable of reducing the incidence of disease and promoting overall health (Chen et al., 2013). The bioactivity of fatty acids for example, depends on the chain length and degree of unsaturation. Long chain, saturated fatty acids, are generally not considered bioactive. Links have been found between saturated fats and increase risk of disease such as coronary heart disease (Li et al., 2015). Conversely, certain shorter chain, unsaturated fatty acids can exert bioactive effects. In addition to mono- and polyunsaturated fatty acids exhibiting health promoting effects, they can increase the absorption of fat-soluble vitamins further benefiting human health (Y. Zhang et al., 2021). Recently, researchers found the *in vivo* examination of food derived bioactive lipids to be a source of interest. At present, *C. elegans* is being used as models to examine how food derived bioactive lipids might exert their bioactivities in the human body (Table 1).

For example, a commercial plant sterol-enriched beverage was supplemented into the diet of *C. elegans* caused an increase in the lifespan of the nematodes (López-García et al., 2020). It was hypothesized that this increase in lifespan was due to an increased resistance to oxidative stress, therefore the researchers exposed the nematodes to both acute and chronic oxidative stress. Under acute oxidative stress, the *C. elegans* fed the lipid-enriched (0.6 g/100 mL) beverage lived 15–17% longer than the controls under the same oxidative stress conditions. Similarly, under H_2O_2 oxidative stress, the nematodes fed the sterol enriched beverage lived 11–20% longer than the controls (López-García et al., 2020). Deuterated polyunsaturated fatty acids have also been suggested for food supplementation to combat oxidation. Using a *C. elegans* model, these lipids were able to decrease ROS levels as well as the number of lipid peroxides created (Beaudoin-Chabot et al., 2019). Similarly, when *C. elegans* were exposed to phytoecdysteroid-enriched quinoa seed leachate (20-hydroxyecdysone), ROS were decreased by 20% compared to the non-exposed nematodes (control) (Graf et al., 2017). Although not many studies on using lipids as antioxidants have been conducted *in vivo* compared to other bioactive compounds, there is still solid evidence that many lipids do display antioxidant activities in *C. elegans*.

Although lipids are the major cause of fat accumulation and obesity, certain lipids can also contribute to protection against obesity, these properties are also being studied in *C. elegans*. One such example is borage seed (*Borago officinalis)* oil, is known to be a natural source of omega-6 fatty acids, a commonly known bioactive lipid. Its anti-obesity properties were discovered when the oil from this seed was supplemented into the environment of *C. elegans*, its anti-obesity properties were discovered. Through Red Nile staining, it was observed that 500

μM of this oil significantly reduce fat content of *C. elegans* (Navarro-Herrera et al., 2018a,b). This study confirmed that natural sources of omega-6 fatty acids could be potent anti-obesity agents *in vivo*. In a different study, transgenic fat-1 *C. elegans* were exposed to dihomo-gamma-linolenic acid, resulting in significant ($p < 0.05$) reduction in lipid droplet accumulation and triglyceride accumulation. This was attributed to an increase in peroxisomal fatty acid β-oxidation (Navarro-Herrera et al., 2018a,b). Similarly, conjugated linoleic acid was able to lower fat accumulation in *C. elegans* by 29%. This activity is attributed to conjugated linoleic acids ability to modulate sir-2.1, a gene with a homolog in humans, silent mating type information regulation 2 homolog (SIRT1) (Shen et al., 2018).

7. Challenges of using *C. elegans* as an *in vivo* model

As with many other *in vivo* models, the use of *C. elegans* comes with its challenges. The most prominent one being contamination. Contamination can originate from the NGM plates, the *E. coli* OP50 stock solution, or airborne particles (Fay, 2013). As the nematodes typically grow on agar, a medium favorable to many contaminants, it is not uncommon to have bacterial, yeast, or mold growth. To avoid contamination of the medium, precautions must be taken when handling nematodes and all the experimental materials. Ideally, all *C. elegans* experimentation should be conducted in a sterile hood. Once a stock of nematodes is contaminated, they should not be used for experimentations until they are cleaned.

For instance, new NGM plates should be made, the *E. coli* OP50 stock must be replaced with fresh stock, and work in a sterile hood or near a Bunsen burner to limit airborne contaminants. If the contaminant is bacterial or yeast in nature, the worms can be cleaned by synchronization with a hypochlorite solution, leaving a clean population of eggs to regrow a stock solution. When contamination is caused by mold, repeated chunking (placing a small piece of NGM containing nematodes on a new plate with fresh NGM) will eliminate the contaminant (Stiernagle, 1999). In addition to the challenges encountered by contamination, accurately determining when the nematodes are deceased and when they are alive can also be difficult. For example, researchers will consider a nematode to be dead when its body is completely straight (Moy et al., 2009). However, nematodes can be completely straight during the process of senescence and may not be completely dead yet; upon prodding with wire, the nematode will move slightly, indicating that it is still alive. Therefore, if an experiment requires 100% accuracy for the time of death of the nematodes (e.g., during acute toxicity assays), a wire prodding technique should be implemented to ensure that a straight nematode is indeed deceased (Sutphin and Kaeberlein, 2009). Lastly, although *C. elegans* have homologs for about 60–80% of human genes, it is important to note that they cannot model all processes in the human body (Kaletta and Hengartner, 2006). In some cases, a higher organism may be needed in order to model a specific process. Despite these potential challenges, *C. elegans* can still be an excellent option to study the bioactive properties of food compounds if preventative measures to avoid contamination are maintained during all stages of experimentation.

8. Conclusion and future directions

C. elegans have proven to be a useful model to conduct preliminary studies of many diseases and disorders because of the high level of gene conservation between *C. elegans* and humans. Compared to other *in vivo* models such as mice and rats, *C. elegans* have the advantage of being less expensive, faster, and relatively easier to grow and cultivate. Researchers are now finding that *C. elegans* are also a useful model to study the bioactive effects of food derived components. Antioxidant activity of food components is one of the most widely studied bioactivities, which often leads to the modulation of the insulin/IGF-1 signaling pathway most commonly an upregulation of the daf-16, the ortholog of the FOXO gene family. Similarly, anti-obesity and anti-aging effects are commonly studied using *C. elegans* as a model. Moving forward, *C. elegans* will likely be used more frequently to conduct *in vivo* preliminary studies on the anti-cancer, antimicrobial, and neuroprotective effects of food derived compounds. Some studies involving different food-derived carbohydrates, fatty acids, proteins, and phenolic compounds have successfully used *C. elegans* to study these main bioactivities, as seen in Table 1, proving the effectiveness of *C. elegans* as a starting model to assess these bioactive properties. *C. elegans* can also be used to draw sound conclusions on the biological activity that food bioactives have on the human body after consumption, including for drug discovery purposes. Since these nematodes model many human processes, they can be used as preliminary models to determine how a drug may function in a living organism before further investing funds into other more expensive *in vivo* models. *C. elegans* remain a promising versatile and relatively simple model to determine biological activity of food components and how these components may interact with the human body upon consumption.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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