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Review

Effects of Vegetal Extracts and Metabolites against Oxidative Stress and Associated Diseases: Studies in *Caenorhabditis elegans*

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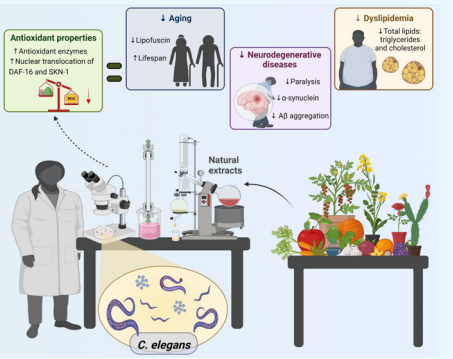
ABSTRACT: Oxidative stress is a natural physiological process where the levels of oxidants, such as reactive oxygen species (ROS) and nitrogen (RNS), exceed the strategy of antioxidant defenses, culminating in the interruption of redox signaling and control. Oxidative stress is associated with multiple pathologies, including premature aging, neurodegenerative diseases, obesity, diabetes, atherosclerosis, and arthritis. It is not yet clear whether oxidative stress is the cause or consequence of these diseases; however, it has been shown that using compounds with antioxidant properties, particularly compounds of natural origin, could prevent or slow down the progress of different pathologies. Within this context, the *Caenorhabditis elegans* (*C. elegans*) model has served to study the effect of different metabolites and natural compounds, which has helped to decipher molecular targets and the effect of these compounds on premature aging and some diseases such as neurodegenerative diseases and dyslipidemia. This article lists the studies carried out on *C. elegans* in which metabolites and natural extracts have been tested against oxidative stress and the pathologies associated with providing an overview of the discoveries in the redox area made with this nematode.



1. INTRODUCTION

Oxidative stress is a physiologic process related to aging and various diseases as causes or consequences. It is defined as an imbalance between oxidants and antioxidants in favor of the former, which leads to an interruption of cell signaling and redox control.[1] Most known oxidants are reactive oxygen and nitrogen species (ROS and RNS, respectively), which include hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet-}$) and hydroxyl ($^{\bullet}OH$) radicals, hypochlorite (ClO^-) and peroxynitrite ($ONOO^-$) anions, and nitric oxide ($NO^{\bullet}$).

Mitochondria is the leading ROS source due to electron leaks in the respiratory transport chain. Also, ROS and RNS are produced in the plasma membrane, cytosol, peroxisomes, and endoplasmic reticulum.[2] The main enzymatic systems involved in ROS production are cytochrome P450, NAD(P)H oxidases (NOX), lipoxygenases, monooxygenases, and nitric oxide synthase (NOS). Furthermore, ROS can be generated through the Fenton reaction and from external stressor factors, such as ultraviolet (UV) radiation or chemical agents.[3] ROS have relevant physiological functions at low levels as signaling molecules; however, their accumulation leads to biomolecule damage, leading to cell death and tissue lesions.[4,5]

In recent years, ROS have been related to various diseases, such as cancer,[6,7] diabetes,[8] atherosclerosis,[9] obesity,[10] arthritis,[11] and neurodegenerative diseases.[12] In some of these pathologies, oxidative stress is a consequence of pathogenesis processes. For instance, during the inflammatory response that follows tissue damage, NOX causes an increase in $O_2^{\bullet-}$ and H_2O_2.[13] In other cases, oxidative stress participates in the development of these pathologies and can accelerate disease progression and exacerbate disease symptoms. The increase in ROS modifies signaling pathways and alters multiple biological processes by modifying proteins, modulating inflammation and survival processes, and dysregulating autophagy.[14] Oxidative stress is also related to premature aging.[15] As a matter of fact, the oxidative stress theory of aging considers that functional loss related to aging is a consequence of the accumulation of ROS damage.[16]

On the other hand, traditional medicine occupies a relevant role in medicine. The World Health Organization (WHO) defines traditional medicine as the knowledge, skills, and practices based on theories, beliefs, and experiences from different cultures used for health maintenance, as well as for prevention, diagnosis, and treatment of physical and mental diseases.[17] Traditional medicine is recognized as a fundamental

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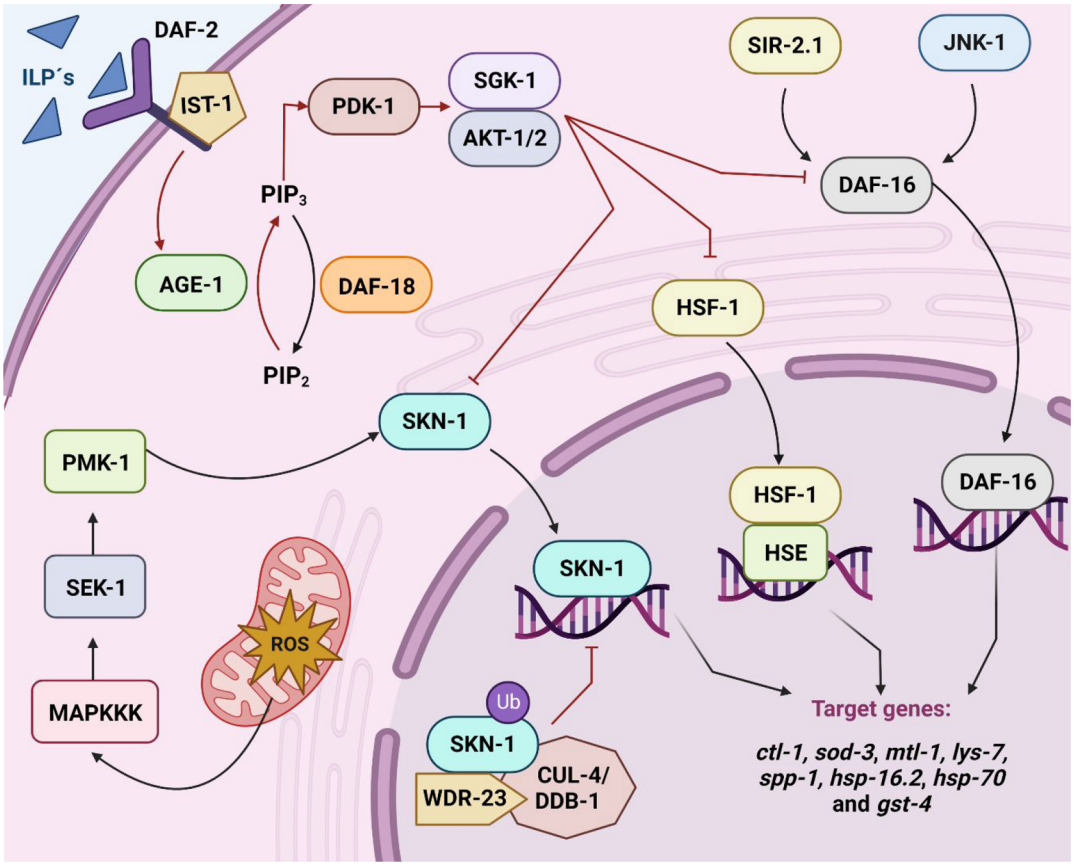

Figure 1. Scheme of the IIS and SKN-1/Nrf2 pathways in *C. elegans*. Activation of the IIS pathway inhibits the nuclear translocation of SKN-1 and DAF-16 (homologous with human forkhead transcription factor/FOXO) and the transcriptional regulator of heat shock factor (HSF-1). However, DAF-18 (human tumor suppressor homologue/PTEN) is antagonistic to this pathway, and its activation induces the nuclear translocation of these transcription factors. In addition, SKN-1 can be activated by activating the MAPK kinase kinase (MAPKKK) cascade and inhibited by proteasomal degradation by the action of the ubiquitin ligase CUL-4/DDB-1. AGE-1: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic alpha subunit homologous. AKT-1/2: protein kinase B 1 and 2. DAF-2: insulin/IGF-1 receptor (IGFR) homologous. HSE: heat shock element. IST-1: insulin receptor (IRS). JNK-1: c-Jun N-terminal kinase homologous. MAPK: mitogen-activated protein kinase. PDK-1: 3-phosphoinositide-dependent protein kinase 1. PMK-1: orthologue of MAPK11 mitogen-activated protein kinase 11. SEK-1: SAPK/ERK kinase. SGK-1: glucocorticoid-inducible kinase-1. SIR-2.1: NAD^+-dependent histone deacetylase homologous. WDR-23: WD repeat protein. Created with biorender.com. Accessed on 31 October 2022 (published with permission from biorender.com; our agreement number is CR24ULKBY2).

resource for the health of millions of human beings. There exists a worldwide interest in traditional medicine usage. For example, 40% of Chinese pharmacological therapy is traditional medicine, and 65% of the Indian rural population uses medicinal plants to treat their ailments.[18,19]

Moreover, there has been significant interest in natural compounds extracted from medicinal plants for phytopharmaceutical development. These compounds are generated by the secondary metabolism of plants and serve important ecological functions.[20] They can be isolated from different parts of the plant, such as leaves, roots, stems, fruits, and seeds.[21] Since these compounds are found in the plant as a complex mixture, they must be separated and identified. Initially, extraction is carried out employing an organic solvent, the selection of which depends on the compounds to be isolated. Techniques used in isolation include column chromatography and crystallization. Further, methods used for metabolite identification include thin-layer chromatography, nuclear magnetic resonance, and high performance liquid chromatography (HPLC) with mass spectrophotometry.[22]

The secondary metabolites most extensively studied for health-promoting effects are flavonoids, terpenoids, alkaloids, saponins, and phenols.[23] On the other hand, the most studied biological activities include anticarcinogenic, antimicrobial, analgesic, healing, and antioxidant properties.[24] For carrying out studies on these properties, *in vitro* or *in vivo* systems could be employed. In the former, immortalized cell lines or primary cultures are used, while whole animal studies are done in the latter, such as rats, mice, rabbits, fish, and nematodes.

Particularly, studies on the nematode *Caenorhabditis elegans* (*C. elegans*) have increased substantially since Sidney Brenner, in 1963, proposed it as a model to study classic molecular biology problems.[25] Success of this model can be explained by the several advantages it possesses over other models.[26] Some of these advantages include (1) having a small size (~1 mm), which allows work with a lot of nematodes on reduced space; (2) having a short life cycle of 3 days from egg to reproductive adult and a great reproductive capacity of approximately 300 descendants, thus having millions of nematodes in a few days with which experiments could be carried out; (3) possessing a transparent cuticle which allows internal structure observation and facilitates the usage of fluorescent dyes; (4) 60 to 80% of *C. elegans* genes have human homologues, allowing the study of diverse biological processes including oxidative stress, aging, cell death, and signaling pathways, among others; and (5) knockout strains can be easily generated through interference

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RNA technology.[27,28] Furthermore, it has been proposed that *C. elegans* can fill in the gap between *in vitro* and *in vivo* studies since it allows a reductionist high-performance approach and also gives physiologically relevant data derived from a whole animal.[27,29] Hence, this work aims to report evidence on vegetal extracts and isolated metabolite effects against oxidative stress and related pathologies observed in the *C. elegans* model to lead to future studies with natural antioxidants that employ this useful model.

2. REDOX STUDIES PERFORMED ON *C. ELEGANS*

C. elegans is a nematode belonging to the Rhabditidae family. It feeds on microorganisms, including the bacteria *Escherichia coli*. It is a hermaphroditic organism, although less than 0.05% of the total are male specimens. It comprises a stoma (mouth), pharynx, intestines, gonads, and a collagen cuticle. Males have a single gonad, efferent vessels, and a tail specialized for copulation.[30] *C. elegans* is used as a model for various studies, including studies in the area of redox biology. In fact, thanks to *C. elegans*, more information can be obtained about molecular targets, the role of antioxidants in slowing aging or other pathologies, and the association of these effects with oxidative stress.[31] Furthermore, *C. elegans* allows us to explore genes and signaling pathways involved in redox regulation through different strategies, including transgenic strains.

2.1. Oxidative Stress in *C. elegans*. Molecular mechanisms that regulate oxidative stress response are highly conserved in *C. elegans*.[32,33] Insulin and insulin-like growth factor (IGF) signaling (IIS) and nuclear factor erythroid 2-related factor 2 (Nrf2) are the most important antioxidant response pathways (Figure 1).

2.1.1. Insulin and Insulin-Like Growth Factor (IGF) Signaling (IIS). The IIS pathway is activated under favorable nematode conditions, allowing normal development and adult life. In *C. elegans*, this pathway starts when insulin-like peptides bind the tyrosine kinase receptor DAF-2 (IGFR homologue), leading to either direct or indirect activation of the phosphatidylinositol 3-kinase AGE-1. The latter involves DAF-2-mediated recruitment of the insulin receptor substrate (IRS)/IST-1.[34,35] After AGE-1 activation, this kinase produces 3,4,5-phosphatidylinositol trisphosphate (PIP_3) from 4,5-phosphatidylinositol bisphosphate (PIP_2).[32,36] PIP_3, in turn, activates the 3-phosphoinositide-dependent protein kinase 1 (PDK-1), which then phosphorylates and activates protein kinases B (AKT1−2) and serum- and glucocorticoid-regulated kinase 1 (SGK-1).[37,38] These molecules phosphorylate and inactivate DAF-16 (FOXO transcription factor homologous), SKN-1 (Nrf2 homologous), and heat shock transcription factor 1 (HSF-1), impeding their translocation to the nucleus. Nevertheless, under unfavorable conditions, such as oxidative stress, IIS is hampered by DAF-18 (PTEN homologous). Thus, DAF-18 allows DAF-16, HSF-1, and SKN-1 nuclear translocation and expression of their target genes. Target genes of these transcription factors include catalase (*ctl-1*), superoxide dismutase-3 (*sod-3*), metallothionein (*mtl-1*), genes of pathogen bacterial defense (*lys-7*, *spp-1*), genes of chaperones (for instance, heat shock proteins *hsp-16.2*), and glutathione S-transferase 4 (*gst-4*).[39,40] Moreover, DAF-16 can also be activated by NAD^+-dependent histone deacetylase homologous (SIR-2.1) and c-Jun N-terminal kinase homologous (JNK-1).[41,42] Particularly, HSF-1 leads to the expression of chaperone genes whose products are pivotal for *C. elegans* longevity and thermotolerance. For instance, HSP-16.2 levels increase in thermal stress resistance.[28,43,44]

2.1.2. SKN-1 Pathway. SKN-1 belongs to a leucine zipper family of proteins and is a relevant transcription factor for cellular protection since it regulates the expression of genes involved in detoxification, antioxidant response, and proteostasis.[45,46] However, if SKN-1 enters the nucleus of unstressed cells, the WD40 repeat protein (WDR-23) recruits SKN-1, which is ubiquitinated by CUL-4/DDB-1 ubiquitin ligase and undergoes proteasomal degradation.[47] In oxidative stress situations, SKN-1 is activated by the antagonistic effect of DAF18 (described above) and by activating the p38 mitogen-activated protein kinase (MAPK) cascade. In the latter, MAPK kinase kinase (MAPKKK) phosphorylates and activates SEK-1. Subsequently, SEK-1 phosphorylates and activates PMK-1, which phosphorylates SKN-1 at Ser74 and Ser340, causing its nuclear translocation.[48,49]

2.2. Markers Used to Study the Antioxidant Properties of Metabolites and Extracts in *C. elegans*. Currently, there are different approaches to studying the mechanisms and antioxidant effects of metabolites and plant extracts. Among the most used and direct is subjecting *C. elegans* to physical or chemical stress after treatment with the compound to be studied. Furthermore, the ability of the compound to reduce oxidative stress can be assessed by the production of reactive oxygen species (ROS) and the activity and levels of antioxidant enzymes. Likewise, the pathway or mechanisms by which the antioxidant compound could work can be defined, for example, the DAF-16 pathway or the SKN-1 pathway. The latter is done by visualizing fluorescent proteins (GFP) in mutants or by evaluating the levels of mRNA (mRNA) with RT-PCR.[50,51]

2.2.1. Stress Resistance. Subjecting *C. elegans* to different types of stress is the most widely used strategy to define the antioxidant properties of a compound. In these assays, ROS levels in the nematode increase to the point that survival decreases. In general, *C. elegans* is first treated with the compound to be studied and subsequently subjected to the stressor. After a certain time, survival is determined by counting live and dead nematodes, or depending on the objective, nematode development and growth are analyzed.[52] H_2O_2, paraquat, or the juglone redox cycler are the most commonly used chemical stressors; however, other compounds such as *tert*-butyl hydroperoxide (*t*-BOOH) and sodium arsenite have also been used,[53] while temperature changes are the most used physical stressor.

Juglone-Induced Oxidative Stress. The quinone juglone is the most employed compound for determining oxidative stress resistance in *C. elegans*. It is a potent redox cycler with a high capacity to react with oxygen and ROS. Juglone can act as a pro-oxidant or antioxidant, depending on its concentration.[54] It has been reported that juglone can be reduced and forms $O_2^{\bullet -}$.[55]

The most used treatment scheme is exposure to 250 μM juglone for 2.5−3 h;[56−58] however, concentrations from 20 to 1000 μM and different exposure intervals have also been used.[59−61]

Paraquat-Induced Oxidative Stress. Paraquat (PQ) is an efficient herbicide that is highly toxic for humans.[62] PQ has been reported to induce mitochondrial dysfunction and oxidative stress.[63,64] It also produces ROS in a redox cycle, where PQ^{2+} is enzymatically reduced to its cationic radical ($PQ^{+\bullet}$). PQ^{2+} is regenerated when $PQ^{+\bullet}$ reacts with molecular oxygen, forming $O_2^{\bullet -}$. This radical forms H_2O_2 spontaneously

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Table 1. Vegetable Extracts and Phytochemicals with Antioxidant Properties Evaluated in the *C. elegans* Model[a]

Vegetable extracts			
Extract	Treatment scheme	Effects in *C. elegans*: oxidative stress	ref.
Essential oils from *Cinnamomum osmophloeum* and *trans*-cinnamaldehyde and D-(+)-camphor	1, 10, and 20 μg/mL	↑ Resistance to oxidative stress (Juglone) ↑ GST-4 ↑ SOD-3	113
Hypericum perforatum extract	1, 0.1, and 0.01 mg/mL	↑ Thermotolerance = Lifespan	114
Willow bark extract (WBE)	10 mg/mL	↑ Survival ↑ *gcs*-1	104
Dry pomace extract	100 μg/mL	↑ Survival ↓ ROS	115
EPs7630 (aqueous alcoholic extract of the roots of *Pelargonium sidoides*)	50 μg/mL	↑ Resistance to oxidative stress (Juglone); ↑ DAF-16 nuclear translocation ↑ Survival	116
Açaí aqueous extract (*Euterpe oleracea* Mart.) (AAE)	100 mg/mL	↑ Resistance to oxidative stress (H_2O_2) in strain *daf*-16, *jnk*-1, *sek*-1, and *skn*-1; ↑ Resistance to osmotic stress in strain *osr*-1 and *unc*-43; ↑ SH groups under stress conditions; ↓ ROS ↑ GCS-1 ↑ SOD-3 ↑ CTL-1 ↑ GST-7	71
Black tea (*Camellia sinensis*) extract (BTE)	50, 100, or 200 mg/L	↑ Resistance to osmotic stress; ↑ Resistance to oxidative stress (UV radiation); ↑ Thermotolerance; ↓ ROS ↑ GPx ↑ SOD-3; ↑ *mev*-1 lifespan ↑ *sir-2.1* ↑ *sek*-1	93
Bacopa monnieri	0.1, 0.01, and 0.001 mg/mL	↑ Resistance to oxidative stress (Paraquat); ↑ Thermotolerance ↑ HSP-16.2 ↓ ROS; ↓ Pharyngeal pumping	117
Extract rich in anthocyanins from fruits of *Euterpe precatoria* (EA)	50, 100, and 200 μg/mL	↑ Resistance to oxidative stress (Juglone); ↓ ROS ↑ DAF-16 ↑ *sod-3* ↓ *hsp16.2*	118
Camellia tenuifolia seed oil (TSO) and oleic acid (OA)	TSO: 0.01% and OA: 0.066 mg/mL	↑ Resistance to oxidative stress (Juglona); ↓ ROS ↑ DAF-16	119
Ayurvedic polyherbal extract (PHE) of six herbs: *Berberis aristata*, *Cyperus rotundus*, *Cedrus deodara*, *Emblica officinalis*, *Terminalia chebula*, and *Terminalia bellirica*	0.01 μg/mL	↑ Resistance to oxidative stress (Juglone); ↑ DAF-2 and 16 ↑ SKN-1 ↑ SOD-3 ↑ GST-4 ↓ ROS	58
Turrea fischeri bark extract	25, 50, and 100 μg	↑ Resistance to oxidative stress (Juglone); ↑ Survival ↓ ROS ↑ DAF-16	120
Methanol extract from *Senna singueana*	100 and 200 μg/mL	↓ ROS ↑ Survival; ↑ Resistance to oxidative stress (Juglone)	60
Cassia root methanolic extract	200 μg/mL	↓ ROS ↑ Survival	121
Root extract from *Cassia abbreviata*	200 μg/mL	↓ ROS ↑ Survival	122
Eugenia supra-axillaris leaf methanolic extract	50, 100, and 200 μg/mL	↑ Resistance to oxidative stress (Juglone); ↓ ROS ↓ *hsp-16.2* ↑ DAF-16	123
Myrciaria tenella leaf ethanolic extract	1 and 10 mg/mL	↓ ROS	124
Methanol extract from olive leaves	0.4 mg/mL	↑ Thermotolerance; ↓ ROS ↑ HSP-16.2 ↑ CAT ↑ SOD ↑ GPX ↓ MDA	99
Styphnolobium japonicum hydroalcoholic fruit extract	300 μg/mL	↑ Resistance to oxidative stress (juglone); ↓ ROS ↑ SOD-3 ↓ HSP-16.2	125
Methanolic extracts of *Populus alba* and *Salix subserrata*	50, 100, and 200 μg/mL	↑ Resistance to oxidative stress (juglone); ↓ ROS ↑ *sod-3*	94
Uncaria tomentosa leaf crude extract	40 μg/mL	↑ Resistance to oxidative stress (juglone); ↓ ROS	126
Essential oils from *Mentha piperita* (peppermint), *Mentha spicata* (native spearmint), and *Mentha gracilis* (Scotch spearmint)	10−200 μg/mL	↑ Resistance to oxidative stress (H_2O_2)	95
Baru pulp (*Dipteryx alata* Vogel)	500 and 1000 μg/mL	↑ Resistance to oxidative stress; ↑ Thermotolerance; ↑ Time of life (13.4%); ↑ SOD-3 ↑ DAF-16	127
Powder and encapsulates from *Origanum vulgare*	0.1, 1, 10, 20, and 50 mg/mL	↑ Antioxidant activity	96
Eugenia uniflora leaves	50, 100, and 150 μg/mL	↑ Resistance to oxidative stress (juglone); ↑ Survival ↑ DAF-16	128
Thistle *Cirsium japonicum*	50 and 100 μg/mL	↓ Pumping rate; ↓ ROS ↑ Lifespan	129
Tetrastigma hemsleyanum leaves extract	25, 50, and 100 μg/mL	↑ Survival rate; ↓ ROS ↓ $O_2^{\bullet-}$ ↓ GSH consumption ↑ *sod-3* and 5 ↑ ctl-2 ↑ *hsp*-16.1 ↑ PMK-1/p38 ↑ SKN-1	103
Mormodica charantia L. saponin ethanolic extract	100 μL	↑ Resistance to oxidative stress (H_2O_2, paraquat, and juglone); ↑ SOD ↑ CAT ↑ GSH/GSSG ↑ *sod-3* ↑ *sod-5* ↑ *ctl1* ↑ *ctl2* ↑ *hsp16.1* ↑ *hsp16.2* ↓ ROS ↓ NEFA ↓ MDA	97
Methanolic extract of carrot dietary fiber polyphenols	436 mg/L	↓ ROS	130
Essential oil from *Achyrocline flaccida* by hydrodistillation	3000 μg/mL	↓ ROS	90
Aqueous extract of *Achyrocline flaccida*	1−10 mg/mL	↓ ROS	131

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Table 1. continued

Phytochemicals			
Phytochemicals	Treatment scheme	Effects in *C. elegans*: oxidative stress	ref.
Flavonoids: myricetin, quercetin, kaempferol, and naringenin	100 μM	↑ Lifespan ↓ ROS ↑ DAF-16 nuclear translocation ↑ SOD-3 Quercetin and myricetin: ↓ Protein-carbonyl levels by ∼60% and 50% (p = 0.0261 and p = 0.0185, Student's t test), respectively. Kaempferol or naringenin did not show any significant effect	132
Lignan pinoresinol (component of flaxseed, sesame seeds, and olive oil)	100 μM	↑ DAF-16 nuclear translocation ↑ Thermotolerance (with mev-1)	110
Lignans from *Arctium lappa*: arctigenin, matairesinol, arctiin, (iso)lappaol A, lappaol C, and lappaol F	10 and 100 μM	↑ Survival under oxidative stress (juglone) ↑ DAF-16 nuclear translocation ↑ *jnk*-1 ↓ ROS	133
Flavanone isoxanthohumol (IX): component of hops (*Humulus lupulus L.*)	50, 100, and 200 μM	↑ Thermotolerance ↓ ROS ↑ DAF-16 nuclear translocation ↑ Antioxidant capacity	134
Natural triterpene ursolic acid (3β-hydroxy-urs-12-en-28-oic acid)	25 μM	↓ ROS ↑ *sod-1, 3,* and 5 ↑ *gst-7* ↑ *hsp*-16.2 ↑ *mtl-1* and *2*	135
Lutein extracted from marigold flowers	5 μM	↓ ROS ↑ Survival ↑ DAF-16 nuclear translocation ↓ HSP-16.2	136
Isoliquiritigenin	13−50 μg/mL	↑ Resistance to oxidative stress (heat and juglone) ↑ Survival ↓ HSP-16.2 ↑ HSF-1, SKN-1	137
Chlorogenic acid	1.4 μM	↑ Thermotolerance ↑ HIF-1, HSF-1 HSP-16, and HSP-70 ↑ Autophagy	138
Enteromorpha prolifera polysaccharide	100 and 200 μg/mL	↑ Thermotolerance ↑ SOD ↓ MDA ↓ ROS ↑ SKN-1 ↑ DAF-16	98
Polysaccharide and acidic polysaccharide from root of *Panax ginseng*	1 mg/mL	↑ Resistance to oxidative stress (juglone) ↓ ROS ↓ MDA	100
Polysaccharides from leaves of *Cyclocarya paliurus* extract	10 μL/90 μL *E. coli* OP50	↑ Resistance to oxidative stress (H_2O_2 and paraquat) ↓ ROS ↓ MDA ↓ NEFA ↓GSSG ↑ SOD ↑ CAT ↑ GPX ↑ GSH	92
Polysaccharides of *Conodopsis pilosula*	0.15−0.75 mg/mL	↓ ROS ↑ *hsp-16.2* expression ↑ DAF-16 nuclear translocation ↑ SOD ↑ CAT	139
Polyphenols from *Rosa roxburghii*	20−100 μg/mL	In paraquat-exposed nematodes: ↑ Survival rate ↑ SOD ↑ CAT ↓ ROS ↓ MDA	91

[a]CAT: catalase, CTL-1: human catalase ortholog, DAF-16: orthologue of forkhead box O1human (FOXO1), GCS-1: gamma-glutamylcysteine synthetase, GSH: reduced glutathione, GSH-Px: glutathione peroxidase, GSSG: oxidized glutathione, GST-4: glutathione S-transferase, H_2O_2: hydrogen peroxide, HIF-1: orthologue of endothelial PAS domain protein 1 human (EPAS1), HIF1A: hypoxia inducible factor 1 subunit alpha, HSP: heat shock protein, JNK-1: Jun N-terminal kinase, MDA: malondialdehyde, MEV-1: orthologue of human succinate dehydrogenase complex C subunit (SDHC), MPK-1: orthologue of mitogen-activated protein kinase human (1MAPK1), MTL-1,2: Metallothionein 1 and 2, NEFA: nonesterified fatty acids, OSR-1: osmotic stress resistant, PMK-1: orthologue of human mitogen-activated protein kinase 11 (MAPK11) and mitogen-activated protein kinase 14 (MAPK14), ROS: reactive oxygen species, SEK-1: orthologue of human mitogen-activated protein kinase kinase 6 (MAP2K6), Sir-2.1: orthologue of human sirtuin 1 (SIRT1), SKN-1: orthologue of nuclear factor erythroid 2-related factor 2 (nrf-2), SOD-3: orthologue of human superoxide dismutase 2 (SOD-2), UNC-43: orthologue of human calcium/calmodulin dependent protein kinase II delta (CAMK2D).

or by superoxide dismutase (SOD) activity.[64] Particularly in *C. elegans*, chronic and acute exposure to paraquat has been reported to alter reproduction, lifespan, gene expression, and mitochondrial physiology.[65]

Hydrogen-Peroxide-Induced Oxidative Stress. H_2O_2 is a ROS produced in mitochondria and cytosol by the action of SOD and cytoplasmic oxidases. It is an essential signaling molecule; however, external sources of H_2O_2 and excessive concentrations lead to oxidative stress.[66,67] H_2O_2 leads to the formation of other ROS, DNA oxidative damage, mitochondrial damage, and apoptosis.[68,69]

In addition, recent studies show an increase in $O_2^{\bullet-}$ in endothelial cells exposed to H_2O_2 through uncoupled NOS and NADPH oxidase under static conditions.[70] The most used scheme in *C. elegans* is to expose the nematode to concentrations ranging from 0.4 to 2 mM.[71,72] For detailed information on the resistance technique to H_2O_2 in *C. elegans*, review the work of Possik and Pause.[73]

Stress Induced by Temperature Changes. Any drastic change in the temperature at which *C. elegans* grows causes relevant macromolecule structure and function changes, altering the physiology of the nematodes. In order to assess thermotolerance, nematodes are subjected to high (35−37 °C) or low temperatures (0−4 °C).

At high temperatures, *C. elegans* presents cellular defects such as neuronal degeneration and necrotic cell death.[74] High-temperature stress resistance assays are generally used to identify factors that regulate protein homeostasis, such as HSF-1 and DAF-16.[75] On the other hand, low temperatures increase the total proportion of unsaturated fatty acids, which preserves the fluidity of the cell membrane.[76,77] Therefore, low temperatures are used in assays that need to identify important mechanisms that regulate cold adaptation, including lipid homeostasis.[75] It is important to note that thermotolerance assays require precision in temperature control, as significant variations in survival rates between experiments can be generated by even small fluctuations.

Other stressors that have also been studied are osmotic stress (NaCl: 50−500 mM), hypoxia (<0.2% O_2), hyperoxia (60% O_2), ultraviolet radiation (254 nm: 10−30 Jm^2/min), endoplasmic reticulum stress (tunicamycin: 5−50 μg/mL and dithiothreitol: 3−5 mM), and heavy metal stress ($CdCl_2$: 30 μM−7 mM, $NaAsO_2$: 100 μM−1 mM, $CuCl_2$: 4 mg/mL, $ZnSO_4$: 0.4−49.5 mM).[75] Finally, it is important to point out that nematodes can respond differently to different stressors; a strain can show greater resistance to oxidative stress with a specific type of stressor and not show a difference with another type of stressor. The response to the tests will depend on the primary type of ROS to which the nematode is exposed (for

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Table 2. Chemical Structure and Bioactivity of Phytochemicals[a]

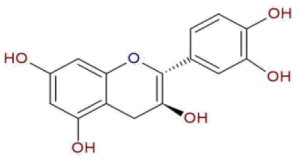
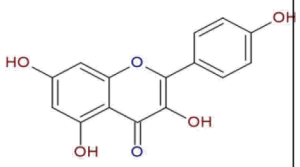
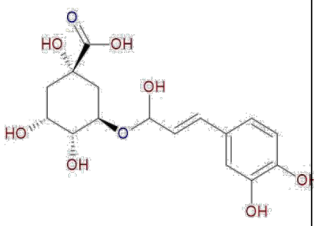
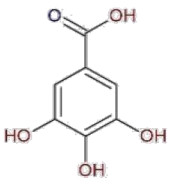
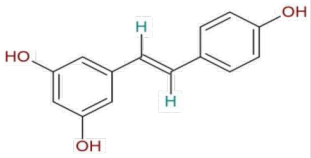
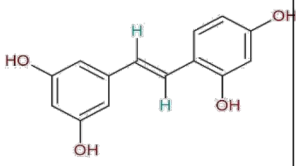
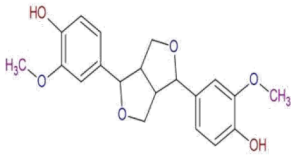
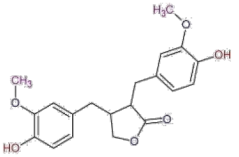
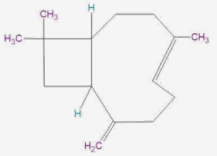
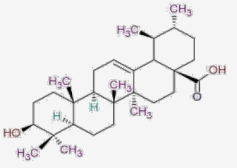
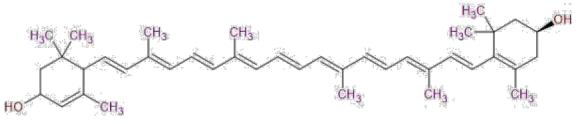
Phytochemical		Bioactivity	Example(s)		Ref.
Polyphenols	Flavonoids	Antioxidative Free radical scavenging capacity Hepatoprotective Antiinflammatory Antiviral	Catechin 	Kaempferol 	140
	Phenolic acids	Antioxidant Antimicrobial Antitumoral Antiallergic Antiinflammatory Antidiabetic	Chlorogenic acid 	Gallic acid (GA) 	141
	Stilbenes	Antimicrobial Antioxidant	Resveratrol 	Oxyresveratrol 	142
	Lignans	Antitumoral Antimitotic Antiviral	Pinoresinol 	Matairesinol 	143
Terpenoids		Provitamin A activity Antitumoral Antioxidant	Beta-caryophyllene 	Ursolic acid 	144
Carotenoids (xanthophylls)		Antioxidant Prevent photochemical damage Provitamin A activity	Lutein 		145

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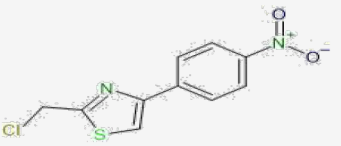
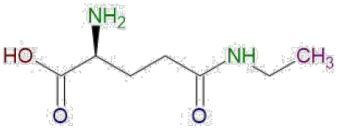
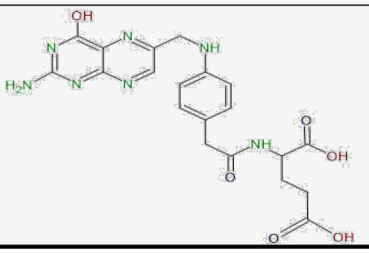
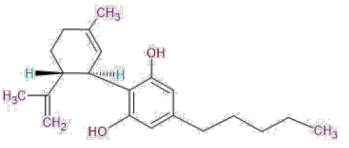
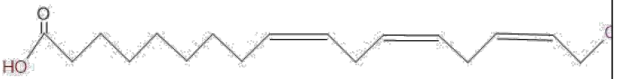
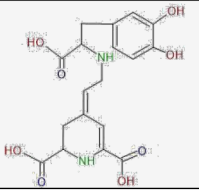
Table 2. continued

Phytochemical	Bioactivity	Example(s)	Ref.
Polysaccharides	Antioxidants Antihypoglycemic Antiinflammatory Antimicrobial Immunomodulatory	Astragalus polysaccharide 	146
Amino acids	Neuroprotection Antidiabetic Antitumoral Antidepressant Antioxidant	L-Theanine 	147
Vitamins	Antioxidant Neural development	Folic acid 	148
Terpenophenols	Antioxidant Antiinflammatory Anxiolytic Antidepressant Antipsychotic	Cannabidiol 	149
Alkaloid	Antioxidant Antiinflammatory Immunomodulatory	Caffeine 	150
Fatty acids	Antioxidative Antiinflammatory Regulation of blood pressure Improved hyperglycemia, hypertriglyceridemia, and insulin resistance	α-linolenic acid 	151
Betalains	Antioxidant Antitumor Chemoprevention Neuroprotective Antimalarial Antimicrobial	Indoline carboxylic actid-betacyanin  Dopaxanthin 	152

[a]Chemical structures made with ACD/ChemSketch software.

example, $O_2^{\bullet-}$, H_2O_2), the rate of exposure (acute or chronic), and the subcellular compartment that is being affected (for example, paraquat primarily damages mitochondria).[64] In addition, the nematode may respond differently depending on the stage of development in which it is found.[78]

2.2.2. ROS Measurement. Measurement of intracellular ROS levels is central in studies of antioxidant properties. These assays indicate if the evaluated extract or compound reduces ROS. For this, it is important that after treating the nematodes with the compound with possible antioxidant activity they are

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subjected to a source of oxidative stress, such as those mentioned in the previous point. Subsequently, the levels of ROS produced by the stressor are determined as well as the effect of the compound of interest in these levels.

ROS levels are usually measured using fluorescent dyes such as 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA), MitoTracker red, and MitoSOX.[28] Most studies use DCFH-DA, a cell-permeable probe that produces fluorescence after intracellular esterases deacetylate, producing DCFH, which is further oxidized, thus forming the fluorescent compound DCF. This probe is sensitive to H_2O_2, $^{\bullet}HO$, and peroxyl ($ROO^{\bullet}$). Nevertheless, it cannot detect $O_2^{\bullet-}$, $NO^{\bullet}$, and hypochlorous acid (HOCl),[79] while MitoTracker CM-H2XRos and MitoSOX are probes focused on ROS produced in mitochondria. MitoSOX is a dihydroethidium (DHE) molecule that is oxidized by $O_2^{\bullet-}$ to form fluorescent ethidium. Furthermore, it has been seen that cellular components such as cytochrome C can also oxidize DHE.[80] The MitoTracker CM-H2XRos red probe is a reduced rosamine oxidized by different ROS, mainly H_2O_2.[81]

2.2.3. Antioxidant Enzyme Activity. Currently, it is known that antioxidants can be direct if they undergo redox reactions and eliminate ROS or RNS and indirect if they activate Nrf2/SKN-1 and the transcription of their target antioxidant enzymes.[82] Therefore, determining the activity of antioxidant enzymes helps to decipher the mechanisms by which a compound of interest exerts its antioxidant functions. Colorimetric assays mainly measure the activity of the different antioxidant enzymes. SOD enzyme activity can be assessed spectrophotometrically by examining formazan decolorization using the enzymatic reaction between xanthine and xanthine oxidase or through $O_2^{\bullet-}$-induced inhibition of lucigenin chemiluminescence.[83,84] Catalase activity is measured by monitoring 240 nm of the disappearance of H_2O_2,[85] while the activity of the enzyme glutathione peroxidase (GPx) is determined by the oxidation of GSH coupled to its turnover by glutathione reductase (GR), where the disappearance of NADPH at 340 nm is monitored.[86]

Antioxidant proteins are also measured using transgenic *C. elegans* that express green fluorescent proteins (GFPs). Among the most used strains is the strain for *sod-3*: CF1553:muIs84 (*sod-3*::GFP+rol-6) and *gst-4*: CL2166:dvIs19 [pAF15(*gst-4*::GFP::NLS)]. Enzyme levels can also be assessed by quantitative polymerase chain reaction (q-PCR).[87−89]

2.3. Effects of Metabolites and Natural Extracts against Oxidative Stress in the *C. elegans* Model. *C. elegans* has been an excellent model to evaluate the antioxidant properties of many phytochemicals (fatty acids, polyphenols, polysaccharides, among others) and extracts, mostly ethanolic and methanolic extracts from various plants, including *Camellia sinensis*, *Populus alba*, *Mentha piperita*, *Origanum vulgare*, *Achyrocline flaccida*, and *Cyclocarya paliurus*.[90−96] A search was done in PubMed with the words "*C. elegans* and plant antioxidants" in 2011−2022. Table 1 lists the studies focused solely on evaluating the antioxidant properties of different plant extracts and phytochemicals. In summary, Table 1 shows that most of the studied phytochemicals and extracts exert antioxidant properties by reducing ROS production, which is related to excellent resistance to different stressors.[71,94,97,98] However, the reported results do not show a common mechanism of action attributable to all phytochemicals and extracts. Since it is observed that the mechanism of action can be through the IIS pathway, the activation of SKN-1 through MAPK, or both. In addition, many of these compounds decrease oxidant stress markers such as malondialdehyde (MDA), which is one of the end products of polyunsaturated fatty acid peroxidation in cells and functions as a marker of oxidative damage to lipids.[91,92,98−101] Some extracts, including *Auricularia auricula*, *Tetrastigma hemsleyanum* leaves, and *Mormodica charantia L.*, have also been shown to increase glutathione (GSH) levels, the primary thiol in the antioxidant response.[92,97,102,103] In addition, willow bark extract, *Euterpe oleracea* Mart, increased γ-glutamylcysteine synthetase (GCS-1), an enzyme involved in GSH synthesis.[71,104]

The difference between the mechanisms of action of the different plant extracts is easily explained because the extracts have active metabolites with different bioactivity, as observed in Table 2. The active metabolites of the plants correspond mainly to phytochemicals such as polyphenols (flavonoids, phenolic acids, lignans, and stilbenes), fatty acids, polysaccharides, saponins, and betalains. Each compound has a characteristic chemical structure, possibly responsible for its antioxidant properties.[105−107] For example, the aromatic amino groups of betalains have been reported to be able to stabilize free radicals. Furthermore, free radicals are stabilized by resonance: the π system of the double bond interacts with the σ bond of the substituent, making the alkyl group of the C═C double bond an electron donor for the π system.[108] Similarly, phenols are prone to enter into efficient electron-donating reactions with oxidizing agents because they are intrinsically electron-rich compounds.[108] Particularly, the *ortho*-catechol group (3′,4′-OH) in the B ring of quercetin (flavone) and catechin (flavanol) is a determinant of a high antioxidant capacity.[109] In addition, the different (sometimes contradictory) results obtained by different authors are also explained by the variety of existing methods, as well as the assay conditions used; more studies are needed to obtain a clear understanding of the mechanisms and molecules involved in this process and the antioxidant effects and pathways of biological activities in organisms.

Finally, it should be noted that there are studies that have begun to evaluate the antioxidant effects of phytochemicals and extracts in the mitochondria, which, as mentioned above, is one of the main sites of ROS production. This has been done using transgenic strains of *mev-1*. *mev-1* is the orthologue of the C subunit of the human succinate dehydrogenase complex (SDHC) involved in several processes, including the defense response to another organism, mitochondrial electron transport, and regulation of the response to oxidative stress.[93,110−112] However, more studies on *C. elegans* focused on studying antioxidant effects on the prevention of mitochondrial dysfunction are lacking. It is expected that in subsequent years there will be new methodological developments and advances in knowledge in the field, for which *C. elegans* should continue to present itself as a convenient and valuable model.

3. COMPOUNDS AND EXTRACTS USED AGAINST AGING AND PATHOLOGIES ASSOCIATED WITH OXIDATIVE STRESS IN *C. ELEGANS*

During the PubMed search with the words "*C. elegans* and plant antioxidants" (2011−2022), studies were separated where the objective was to associate the antioxidant properties of metabolites and natural extracts with conditions related to oxidative stress, such as aging, neurodegenerative diseases, obesity, and dyslipidemia. In most of these studies, extracts of

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Table 3. Vegetable Extracts and Phytochemicals with Antioxidant Properties against Aging in the *C. elegans* Model[a]

Vegetable extracts				
		Effects		
Extract	Treatment scheme	Oxidative stress	Aging	ref.
Humic substances with hydroxybenzene moieties	0, 0.2, 0.4, and 2.0 mM dissolved organic carbon (DOC)	↑ Thermotolerance	↓ Growth ↓ Reproduction↑ Pharyngeal pumping	164
Rooibos tea extracts (*Aspalathus linearis*) with acetic acid	10, 20, and 50 μM	↑ Resistance to oxidative (juglone) ↓ ROS ↑ DAF-15 ↑ SOD-3 ↑ HSP-3	↑ Lifespan	165
Alpinia zerumbet leaf extract (ALP)	100 mM	↑ Resistance to oxidative stress (H_2O_2) ↑ SOD-3 ↑ HSP-16.2	↑ Lifespan	166
Anthocyanin-rich methanolic extract of purple wheat	100 μg/mL	↑ DAF-16 translocation with thermal stress ↓ *hsp-16.2* in oxidative stress by juglone ↓ ROS	↑ Lifespan	167
Whole apple extracts with acetone	2.5, 5, and 10 mg/mL	↑ Resistance to oxidative stress (paraquat, UV, and pathogenic infection with *P. aeruginosa*)	↑ Lifespan ↑ Healthspan ↓ Lipofuscin	168
Ocimum sanctum crude extract	1 mg/mL	↑ Thermotolerance ↓ ROS	↑ Lifespan	169
Wheat gluten hydrolyzate (WGH)	0.1−1 mg/mL	↑ Resistance to oxidative stress (paraquat) ↑ Thermotolerance ↓ ROS	↑ Lifespan ↓ Lipofuscin ↑ Locomotion	163
Oranges enriched with β-carotene	1 and 2%	↑ Resistance to oxidative stress (H_2O_2)	↑ Lifespan	72
Hot water extracts from the leaves of *Chamaecyparis obtusa* var. *Formosan*	2 and 20 μg/mL	↑ Resistance to oxidative stress (juglone) ↓ ROS	↑ Lifespan ↓ Lipofuscin	57
Essential oils from the leaves of the mixed-type tree *Cinnamomum osmophloeum*	1.5−200 μM	↑ Resistance to oxidative stress (juglone)	↑ Lifespan ↑ Longevity, according to *daf-16*	170
Aqueous extract of *Ilex paraguariensis*	—	↓ ROS ↑ DAF-16 nuclear translocation	↑ Lifespan	171
Mulberry leaf extract total polyphenols (MLP)	25 mg/L	↑ Resistance to oxidative stress (H_2O_2 and paraquat) ↑ *sod-3* ↑ *lipl-4* ↑ FARD- 1 ↑ FAT-6 ↑ daf-16 ↑ UNC-51	↑ Lifespan ↓ Aging ↓ Fatty acid storage	172
Acanthopanax sessiliflorus aqueous extract	0, 50, 100, 500 y 1000 mg/L	↑ Resistance to oxidative stress (UV radiation) ↑ Thermotolerance	↑ Lifespan	173
Soluble fraction of ethyl acetate from *Vigna angulariz*	50 and 100 μM	↑ Resistance to oxidative stress (juglone) ↑ Thermotolerance ↑ Antioxidant enzyme activities (SOD and catalase) ↓ ROS ↑ *hsp-16.2*	↑ Lifespan	174
Ethyl acetate fraction of *Ribes fasciculatum* (ERF)	125, 250, and 500 $\mu g \cdot mL^{-1}$	↑ SOD ↓ ROS	↑ Lifespan ↓ Lipofuscin	175
Three extracts of Tsai Tai: *Brassica chinensis*	2 mg/m	↑ Resistance to oxidative stress (paraquat) ↓ ROS ↓ MDA ↑ SOD	↑ Lifespan	176
Methanol extract from the heartwood of *Caesalpinia sappan*	50 and 100 μM	↑ Resistance to oxidative stress (juglone) ↑ Resistance to osmotic stress (NaCl) ↑ Thermotolerance ↑ *sod-3* ↑ HSP16.2 ↓ ROS ↑ SOD	↑ Lifespan	61
Polygonum mulltiflorum extract	1000 μg/mL	↑ Resistance to oxidative stress (paraquat) ↓ ROS ↑ DAF-16	↑ Lifespan ↓ Lipofuscin	160
Ethanol extract from *Agrimonia procera* Wallr.	50, 100, and 200 μg/mL	↓ ROS ↑ Resistance to oxidative stress (paraquat) ↑ Thermotolerance	↑ Lifespan	177
Paullinia cupana (guarana) ethanolic extract	100, 500, and 1000 μg/mL	↑ DAF-16 ↑ HSF-1 ↑ SKN-1	↑ Lifespan	178
Water extract from *Calcycophyllum spruceanum*	200 and 300 μg/mL	↑ Resistance to oxidative stress (juglone) ↓ ROS	↑ Lifespan ↑ Pharyngeal pumping	179
Lowbush cranberry	50 and 400 μg/mL	↑ DAF-16	↑ Lifespan	180
Blueberry extract	50, 100, and 200 mg/mL	↑ Resistance to oxidative stress (paraquat, heat, and UV radiation) ↑ Thermotolerance ↑*sod-3, cat-1, mev-1, skn-1, mek-1, nhr-8*, and *daf-16*	↑ Lifespan ↓ Lipofuscin	111
Opuntia fruit and pure betalains	10, 25, 50, and 100 μM	↑ Resistance to oxidative stress (juglone)	↑ Lifespan	181
Damaurone D from damask rose	5, 10, 15 μM	↑ Resistance to oxidative stress (paraquat and NaCl) ↓ ROS ↑ SOD ↑ CAT	↑ Lifespan ↓ Food intake ↓ Body length ↓ Lipofuscin	182
Purple pitanga fruit (*Eugenia uniflora*) ethanolic extract	100, 250, and 500 μg/mL	↑ Resistance to oxidative stress (H_2O_2 and juglone) ↓ ROS ↑ SOD	↑ Lifespan	183
Cleistocalyx nervosum var. *Paniala*	1−100 μg/mL	↑ DAF-16 ↓ ROS ↓ *daf-2* ↓ *age-1*	↑ Lifespan ↓ Lipofuscin	161

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Table 3. continued

Vegetable extracts				
		Effects		
Extract	Treatment scheme	Oxidative stress	Aging	ref.
Jatu-phala-Tiga polyherbal infusion (*Phyllanthus emblica*, *Terminalia arjuna*, *Terminalia chebula*, and *Terminalia bellirica*)	5 mg/mL	↑ Resistance to oxidative stress (H_2O_2)	↑ Lifespan	184
Glochidion zeylanicum leaf hexane and methanolic extracts	25, 50, and 100 μg/mL	↓ ROS ↑ SOD-3 ↑ GST-4 ↓ HSP-16.2	↑ Lifespan ↑ Pharyngeal pumping	185
Liangyi Gao	1 mg/mL	↑ Resistance to oxidative stress (H_2O_2) ↑ Thermotolerance ↑ *daf-16* ↑ *sod-3* ↑ *sir-2.1*	↑ Reproduction ↑ Pharyngeal pumping ↑ Motility ↑ Growth	186
Anacardium oxxidentale leaf extracts	25, 50, and 100 μg/mL from hexane and dichloromethane extract and 1, 2.5, and 5 μg/mL from methanolic extract	↓ ROS ↑ *sod-3* ↑ *gst-4*	↑ Longevity ↑ Pharyngeal pumping ↓ Lipofuscin ↑ Lifespan	187
Endopleura uchi water extract from the stem bark	299 μg/mL	↑ Resistance to oxidative stress (juglone) ↓ ROS ↑ *sod-3* ↓ *hsp-16.2*	↑ Lifespan	188
Holothuria leucospilota n-butanol fraction	10, 100, 500, and 1000 μg/mL	↑ Resistance to oxidative stress (UV radiation) ↑ Thermotolerance ↑ DAF-16	↑ Lifespan ↓ Lipofuscin	189
Diplicyclos palmatus methanolic leaf extract	200−1000 μg/mL	↑ Resistance to oxidative stress (UV-A radiation)	↑ Lifespan	190
Caesalpinia mimosoides leaf extract	25, 50, and 100 μg/mL	↑ Resistance to oxidative stress (juglone) ↓ ROS	↑ Lifespan ↓Aging pigments	191
Zymolytic grain extract	3.25 and 6.5 mg/mL	↑ Thermotolerance ↑ Resistance to oxidative stress (UV-radiation)	↑ Lifespan	192
Rosa rugosa aqueous polyphenol extract	25, 50, 100, and 200 μg/mL	↑ Thermotolerance ↑ Resistance to oxidative stress (UV-radiation)	↑ Lifespan	193
Licorice (*Glycyrrhiza glabra*) roots ethanolic extract	250 μg/mL	↑ Resistance to oxidative stress (juglone)	↑ Lifespan	194
Butiá fruit extract (*Butia eriospatha*)	50, 250, and 500 μg/mL	↑ Resistance to oxidative stress (H_2O_2)	↑ Lifespan	195
Naringin dissolved in PBS	50 μM	↓ ROS	↑ Lifespan ↓ Lipofuscin	196
Fruits of mangrove *Sonneratia apetala*	300 μM	↑ Thermotolerance	↑ Lifespan	197
O-Acetylglucomannan from roots of *Llium davidii* var. *unicolor Cotton*	1 and 4 mg/mL	↑ Thermotolerance ↓ ROS ↑ SOD ↑ CAT ↓ MDA	↑ Lifespan ↑ Reproduction duration ↓ Lipofuscin	162
Tart cherry extract	6 and 12 μg/mL	↑ *sod-2*, *skn1* ↑ Spare respiration	↑ Lifespan ↑ *daf-16*, *daf-18*, and *aak-2*	198
Orange extracts	100, 200, and 400 mg/mL	↑ Resistance to oxidative stress (UV radiation) ↑ Thermotolerance ↓ ROS ↑ CAT ↓ MDA ↑ *daf-16* ↑ *sod-3* ↑ *gst-4* ↑ *sek-1* ↑ *skn-1* ↓ *age-1*	↑ Lifespan ↑ Motility ↓ Accumulation of age pigment ↑ Survival ↑ Healthspan	199
Astragaloside IV from *Astragali radix*	5 μM	↑ Thermotolerance ↑ SOD ↑ CAT ↑ *ctl-2* ↑ *ctl-3*	↑ Lifespan ↑ Movement capacity	200
Polysaccharide hydrolyzates from pumpkin	4 mg/mL	↑ Resistance to oxidative stress (methyl viologen) ↓ ROS	↑ Lifespan	201
Ethanoic extract of *Paullinia cupana* seeds	100−500 μg/mL	↓ Resistance to oxidative stress (juglone)	↑ Lifespan	202
Onion vinegar	1 mL	↑ GPx ↑ CAT ↑ SKN-1 ↓ ROS ↑ Survival under sodium arsenite-induced oxidative stress	↑ Lifespan	203

Phytochemicals				
		Effects		
Phytochemicals	Treatment scheme	Oxidative stress	Aging	ref.
Tannic acid (TA)	25 and 400 μM	↑ Resistance to oxidative (H_2O_2) ↑ Thermotolerance ↑ Antioxidant capacity	↑ Lifespan ↓ Body length	204
Gallic acid (GA)	25 and 800 μM	↑ Thermotolerance	↑ Lifespan ↑ Body length	
Ellagic acid (EA)	25 and 300 μM	↓ Resistance to oxidative (H_2O_2)	–	
Catechin (CT)	25 and 800 μM	↑ Resistance to oxidative (H_2O_2) ↑ Thermotolerance	↑ Lifespan ↓ Body length	
Ferulsinaic acid	500 nM, 10 μM, and 100 μM	↑ Resistance to oxidative stress (paraquat) ↑ Thermotolerance ↓ MDA ↓ AGE	↑ Lifespan	205
Tyrosol: phenol from extra virgin olive oil	250 μM	↑ Thermotolerance ↑ DAF-2 ↑ DAF-16 ↑ HSF-1	↑ Pharyngeal pumping frequency	206
L-Theanine	1 μM	↑ Resistance to oxidative stress (paraquat)	↑ Lifespan	207

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Table 3. continued

Phytochemicals	Treatment scheme	Phytochemicals: Effects: Oxidative stress	Phytochemicals: Effects: Aging	ref.
Myricetin	100 μM	↑ DAF-16 nuclear translocation ↓ ROS	↑ Lifespan ↓ Lipofuscin	158
Resveratrol	50, 100, or 200 μM	↑ Resistance to oxidative stress (juglone)	↑ Lifespan	208
β-Caryophyllene	25, 50, 100, and 500 μM	↑ Resistance to oxidative stress (juglona) ↓ ROS	↑ Lifespan of wild type ↑ Lifespan of *mev-1*, *daf-16*, *eat-2*, *sir-2.1*, and *skn-1* ↓ Pharyngeal pumping frequency ↓ Lipofuscin	112
Derivatives of myricetin (laricitrin, syringetin, and myricetintrimethyl ether)	100 μM	↓ ROS ↑ Thermotolerance ↑ Daf-16 nuclear localization	↑ Lifespan ↓ Lipofuscin	159
Folic acid	10, 25, and 50 μM	↑ GST-4 ↑ SOD-3 ↓ ROS ↓ mTOR ↓ IGF-1 ↑ sir. 2.1 ↑ *daf-16* ↑ *skn-1*	↑ Lifespan ↓ Pharyngeal pumping frequency ↓ Fecundity ↑ Size ↓ Lipofuscin ↑ Increased chemotaxis index	209
Oxyresveratrol and resveratrol	500 and 1000 μM	↓ *daf-16* ↑ sir-2.1	↑ Lifespan ↑ yaak-2	210
Flavonoid baicalein	100 μM	↑ Resistance to oxidative stress (sodium arsenite) ↑ Thermotolerance ↑ SKN-1	↑ Lifespan	211
Chlorogenic acid	5, 10, 500, and 2000 μM	↑ AF-16 ↑ HSF-1 ↑ SKN-1 ↑ HIF-1 ↓ SIR-2.1	↑ Lifespan of *eat-2*, *glp-1*, and *isp-1* mutants	212
Boeravinone B from *Boerhaavia diffusa* L.	25 μM	↓ ROS ↑ GST ↑ SOD-3 ↑ HSP-16.2	↑ Lifespan ↓ Lipofuscin	213
Phytochemicals of *Dioscorea alata* tubers extract	200 and 300 μg/mL	↑ *hsp-16.2* ↑ *hsp-6* ↑ *hsp-60* ↑ *gst-4*	↑ Lifespan	214
Flavonoid from *Radix tetrastigma*	50 μg/mL	↑ SOD ↑ Resistance to oxidative stress (paraquat)	↑ Lifespan ↓ Lipofuscin	215
Betalains: indicaxanthin, indoline carboxylic acid-betacyanin, phenylalanine-betaxanthin, and dopaxanthin	25 μM	↑ DAF-16 ↑ SKN1	↑ Lifespan	216
5-Hydroxy-6.7.8.3′,4′-pentamethoxyflavone	50 μM	↑ Survival after stress induced by juglone ↓ ROS	↑ Lifespan ↓ Lipofuscin accumulation	217

[a]AGEs: Advanced glycation end products, CAE: chlorogenic acid equivalent, CAT: catalase, CTL-1: human catalase ortholog, DAF-16: orthologue of forkhead box O1human (FOXO1), GCS-1: gamma-glutamylcysteine synthetase, GSH: reduced glutathione, GPx: glutathione peroxidase, GSSG: oxidized glutathione, GST-4: glutathione S-transferase, H_2O_2: hydrogen peroxide, HIF-1: orthologue of endothelial PAS domain protein 1 human (EPAS1), HIF1A: hypoxia inducible factor 1 subunit alpha, HSP: heat shock protein, JNK-1: Jun N-terminal kinase, MDA: malondialdehyde, MEV-1: orthologue of human succinate dehydrogenase complex C subunit (SDHC), MTL-1,2: metallothionein 1 and 2, NEFA: nonesterified fatty acids, OSR-1: osmotic stress resistant, PMK-1: orthologue of human mitogen-activated protein kinase 11 (MAPK11) and mitogen-activated protein kinase 14 (MAPK14), ROS: reactive oxygen species, SEK-1: orthologue of human mitogen-activated protein kinase kinase 6 (MAP2K6), Sir-2.1: orthologue of human sirtuin 1 (SIRT1), SKN-1: orthologue of nuclear factor erythroid 2-related factor 2 (nrf-2), SOD-3: orthologue of human superoxide dismutase 2 (SOD2), UNC-43: orthologue of human calcium/calmodulin-dependent protein kinase II delta (CAMK2D).

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Table 4. Representative *C. elegans* Strain Models for Neurodegenerative Diseases[a]

Strain	Transgene product	Expression	Phenotype
		Alzheimer's disease	
CL2006	Amyloid-β 3−42	Body wall muscles	Paralysis and reduced progeny
GMC101	Amyloid-β 1−42	Body wall muscles	Paralysis
CL2355	Amyloid-β 3−42	Pan-neuronal	Reduced lifespan, impaired learning, and chemotaxis
GRU102	Amyloid-β 1−42	Pan-neuronal	Reduced lifespan, muscle defects, and ATP depletion
JKM2	Untagged and mScarlet-tagged amyloid-β 1−42	Pan-neuronal	Reduced lifespan and progeny, muscle defects, motility impairment, neurite deterioration, chemotaxis, and pathogen avoidance impairment
CMD01	Amyloid-β 1−42	BAG glutamatergic neurons	Altered response to elevated CO_2 concentrations
pbLH98	GFP-tagged amyloid-β 1−42	Cholinergic neurons	Nonreported
		Parkinson's disease	
Paex-3:: *αsyn*	α-Synuclein	Pan-neuronal	Dopaminergic neuron loss and movement impairment
Paex-3:: *αsyn (A53T)*	Mutant α-synuclein (A53T)	Pan-neuronal	Dopaminergic neuron loss and movement impairment
Pdat-1:: *αsyn (A56P)*	Mutant α-synuclein (A56P)	Dopaminergic neurons	Dopaminergic neuron neurite defects and basal slowing behavior deficiency
NL5901	α-Synuclein fused to YFP	Body wall muscle	α-Synuclein aggregation and reduced number of body bends

[a]For more details of strains used for neurodegenerative diseases studies, we refer readers to two excellent papers.[219,227]

plants and fruits that are widely known worldwide, such as wheat, oranges, apples, blueberries, roses, cherries, onions, and tomatoes, were tested. Also, compounds isolated from different plants were used, including resveratrol, epigallocatechin 3-gallate, catechin, myricetin, quercetin, oleic acid, tyrosol, and pyronisenol, among others.

3.1. Aging. Aging is a natural process characterized by a time-dependent cellular and functional decline, causing a reduction in the quality of life.[153] Aging is the main risk factor for developing many pathologies, including cardiovascular diseases, cancer, and neurodegenerative diseases (for example, Alzheimer's disease).[154] Therefore, it is of paramount importance to identify therapeutic interventions that delay aging and, at the same time, stop the progression of age-related pathological conditions. Within this context, compounds with antioxidant properties have taken on great importance due to the strong relationship between oxidative stress and premature aging.[155,156]

In particular, *C. elegans* has been a widely used model to study the antiaging effects of a large number of natural extracts and metabolites, thanks to the fact that this nematode has the advantage of having a short life cycle, which allows studies on aging to be carried out in a short time (3 weeks). Lipofuscin is one of the most used markers to determine aging in *C. elegans*. Lipofuscin, also known as the "age pigment", is a non-degradable compound formed by oxidized and cross-linked proteins, lipids, and saccharides. It is produced naturally throughout the nematode's life and accumulates in postmitotic cells as aging proceeds, resulting in age-dependent degeneration of various cellular systems. In addition, lipofuscin accumulation promotes aging since it acts as an inhibitor of the proteasome by binding directly to its complexes.[157] However, it has been seen that many phytochemicals and natural extracts can increase the lifespan of *C. elegans* by reducing the accumulation of lipofuscin, which has also been associated with a decrease in ROS production and more excellent resistance to different types of stressors.[57,158−162] Also, it has been seen that these compounds increase the locomotion and mobility of nematodes affected by the aging process.[163] Table 3 shows the extracts and natural compounds with antioxidant and antiaging properties in the *C. elegans* model.

3.2. Neurodegenerative Diseases. Neurodegenerative diseases are a heterogeneous group of pathologies involving the progressive degeneration of the structure and function of the nervous system. Alzheimer's and Parkinson's diseases are the most prevalent neurodegenerative diseases. Alzheimer's disease is characterized by severe memory deficits and impaired thinking and social skills.[218] On the other hand, Parkinson's disease is a neurological motor disorder that involves impaired balance, bradykinesia, resting tremors, and rigidity, and patients could also present nonmotor symptoms, such as dementia.[219]

Noteworthily, around 50 million people have Alzheimer's, and 6.1 million have Parkinson's globally.[220,221] Moreover, the likelihood of developing a neurodegenerative disease increases with age, and the older population is increasing, with an estimated 1.5 billion older people by 2050.[222] Further, despite treatment for symptom amelioration being available, there is no strategy for halting the progression of these pathologies.[220,221] Therefore, the need for new treatment options is evident. Notably, oxidative stress plays a relevant role in neurodegenerative diseases and could be a therapeutic target.[223] Oxidative stress and the formation of amyloid-β peptide plaques and neurofibrillary tangles (aggregates of tau proteins) are the central mechanisms of the pathophysiology of Alzheimer's disease; these three factors exacerbate each other, ultimately leading to synaptic dysfunction and neuronal death, which causes symptoms of this disease.[224,225] Regarding Parkinson's disease, mitochondrial dysfunction and oxidative stress lead to the death of substantia nigra dopaminergic neurons, which causes the motor deficits characteristic of this pathology.[226] Importantly, plant extracts and isolated vegetal secondary metabolites with antioxidant activity have been proven to exert protective effects in *C. elegans* neurodegenerative disease models. Some nematode strains used as models of these pathologies are shown in Table 4, and antioxidant agents reported to exert protective effects in neurodegenerative nematode models are presented in Table 5.

As mentioned before, the formation of insoluble amyloid-β peptide plaques is a major neuropathological characteristic of

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Table 5. Vegetable Extracts and Phytochemicals with Antioxidant Properties against Neurodegenerative Diseases in the *C. elegans* Model[a]

Vegetable extracts					
			Effects		
Extract	Treatment scheme	Disease	Oxidative stress	Neurodegenerative disease	ref.
Green tea hexane extract and green tea aroma fraction	10 and 100 μg/mL	Alzheimer's disease	↑ Antioxidant activity	↓ Paralysis ↑ Lifespan	233
Methanol extracts of tea seed pomace from *Camellia tenuifolia*	1 and 10 μg/mL	Alzheimer's disease	↓ ROS ↑ Resistance to oxidative stress (juglone)	↑ Lifespan ↓ Amyloid-β toxicity ↓ Paralysis	56
Hydroalcoholic extract of Carqueja	50 mg/mL	Alzheimer's disease	↑ Resistance to oxidative stress induced by *tert*-butyl hydrogen peroxide ↓ ROS ↑ gst-4 ↓ sod-3	↓ Amyloid-β toxicity ↑ Proteasome activity ↑ Heat shock proteins	234
Essential oils of *Zelkova serrata* (Thunb.)	3 and 30 μM	Alzheimer's disease	↑ Resistance to oxidative stress (juglone) ↑ Thermotolerance ↓ ROS	↓ Paralysis	235
Dichloromethane extract from the roots of *Carlina acaulis*	5, 10, and 25 μg/mL	Alzheimer's disease	↑ Antioxidant activity ↑ daf-16 ↑ Resistance to oxidative stress (juglone) ↑ Thermotolerance	↓ Paralysis	236
Pure tea water extract, black tea, and green tea	0.5, 1, and 2 mg/mL	Alzheimer's disease	↓ Paralysis ↑ Resistance to oxidative stress (metal Cr^{6+})	↓ Paralysis ↑ Lifespan	237
Shatavarin IV (SIV): *Asparagus racemosus* (Liliaceae)	12.5, 25, 50, 100, and 500 μM	Parkinson's disease	↓ ROS ↓ protein carbonylation ↑sod-1, sod-2, sod-3, gst-4, gst-7, and ctl-2	↑ Lifespan ↓ α-Synuclein aggregation ↓ Lipid accumulation ↑ Dopamine levels	238
Hydroalcoholic extract from *Cassia fistula*	100, 200, and 300 μg/mL	Alzheimer's disease	↓ ROS ↓ HSP-16.2 ↑ DAF-16 and SOD-3	↓ Polyglutamine ↓ Paralysis	239
Flowers of *Tagetes erecta*	62.5, 125, and 250 μg/mL	Alzheimer's disease	↑ Resistance to oxidative stress (juglone) ↑ Lifespan	↓ Paralysis	240
Guarana (*Paullinia cupana*) hydroalcoholic extract	10 and 5 mg/mL	Huntington's diseases	↑ Lifespan ↑ proteasome activity ↓ ROS ↓ autophagosomes ↑ SOD-3 and HSP-16.2	↓ PolyQ aggregation	241
Decalepis hamiltonii aqueous root extract	2.5 mM	Parkinson's disease	↑ *sod-3*, *gst-2*, and *gst-4* ↑ pharyngeal pumping ↑ NADH-cytochrome C reductase ↓ ROS	↓ Repulsion time ↑ dopamine	242
Zijuan Pu'er tea extract	0.1−0.4 mg/mL	Alzheimer's disease	↑ DAF-16 ↑ SOD-3 ↓ ROS	↓ Amyloid-β accumulation	243
Hibiscus sabdariffa extract	0.5 and 1 mg/mL	Alzheimer's disease	↑ Lifespan ↑ DAF-16 ↑ SKN-1	↓ Amyloid-β-induced paralysis	244
Betula utiliz ethanolic extract	50 μg/mL	Alzheimer's and Parkinson's diseases	↑ Resistance to oxidative stress and thermal ↓ ROS ↑ lifespan	↓ Amyloid-β ↓ α -synuclein aggregation	245
Ilex paraguariensis hydroalcoholic extract	2 and 4 mg/mL	Alzheimer's disease	↓ ROS ↑ lifespan ↑ Resistance to oxidative stress (amyloid beta-peptide (Aβ))	↑ *hsp-16.2* ↑ *hsf-1* and *daf-16* ↓ progression of paralysis ↓ AChE activity	246
Enzymatic-assisted extracts from sweet cherry pomace	100 and 400 μg/mL for oxidative stress resistance, 10−30 μL/mL for enhanced mobility, and nonspecified for effect on paralysis	Alzheimer's disease	↑ Survival rate under H_2O_2 treatment ↓ Age-related decreased mobility	↓ Amyloid β-induced paralysis	247
Lyophilized tomato juice: wild-type and genetically engineered to produce saffron carotenoids	4 mg/mL	Alzheimer's disease	-	↓ Amyloid-β-induced paralysis	248

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Table 5. continued

Phytochemicals	Treatment scheme	Disease	Phytochemicals: Effects: Oxidative stress	Phytochemicals: Effects: Neurodegenerative disease	ref.
Astragalan, an acidic polysaccharide isolated from *Astragalusmembranaceus* l	0.5, 1, 2, and 4 mg/mL	Parkinson's disease	↓ ROS ↓ MDA ↑ SOD, GPx	↑ Lifespan ↓ *egl-1*proapoptotic gene expression ↑ AChE	235
5-Desmethylnobiletin	12.5, 25, and 50 μM	Alzheimer's disease	↓ ROS ↑ Resistance to oxidative stress (Juglone)	↑ ACh ↑ nAChR ↓ AChE ↑ *unc-29* ↓ *ace-2*	249
α-Linolenic acid	5, 10, 20, and 40%	Aldicarb assay	↓ Mitochondrial stress	↑ Level of synaptic acetylcholine and acetylcholinesterase	250
Artemisia pallens sesquiterpenoids	25 and 50 μM	Parkinson's disease	↑ *sod-1*, *-2*, and *-4* transcription	↓ α-Synuclein aggregation ↑ Chemo-repulsion-related locomotion, *pdr-1* transcription (mitochondrial proteostasis)	251
Cannabidiol	25−100 μM	Parkinson's disease	↓ ROS ↑ *sod-3* expression	↓ 6-OHDA-induced dopaminergic neuron loss, alterations in food-sensing behavior, and lifespan reduction ↓ α-synuclein accumulation, reduction of lipid content, and ubiquitin-like proteasome system activity (in an α-synuclein accumulation model)	252
Cannabidiol	100 μM	Alzheimer's disease	↓ ROS ↑ survival under oxidative stress (Juglone)	↓ Amyloid-β aggregation ↓ Amyloid-β-induced paralysis, the decline in pharyngeal pumping rate and body bending, and chemotactic dysfunction	253
Orientin	100 μM	Parkinson's, Alzheimer's, and Huntington's diseases	↑ Survival rate of paraquat-exposed worms ↓ ROS ↑ expression of DAF-16 target genes ↑ SOD-3, SKN-1 ↑ autophagy ↑ proteostasis ↑ lifespan ↓ lipofuscin and age-related body bending reduction ↑ heat and pathogen stress resistance	↓ α-Synuclein accumulation and related reduction in body bending ↓ 6-OHDA-induced dopaminergic neuron loss ↓ Amyloid-β-induced paralysis ↓ Poly-Q aggregation	253

[a]ROS: reactive oxygen species, MDA: malondialdehyde, DAF-16: orthologue of forkhead box O1 human (FOXO1), H_2O_2: hydrogen peroxide, HSP: heat shock protein, SKN-1: orthologue of nuclear factor erythroid 2-related factor 2 (Nrf-2), SOD: superoxide dismutase, GPx: glutathione peroxidase, 6-OHDA: 6-hydroxydopamine, ACh: acetylcholine, AChE: acetylcholine esterase, nAChR: nicotinic acetylcholine receptor, polyQ: polyglutamine, *gst*: glutathione S-transferase genes, *sod:* superoxide dismutase genes, *ctl:* human catalase homologue gene, *hsf:* heat shock transcription factor, *pdr:* E3 ubiquitin-protein ligase parkin.

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Table 6. Vegetable Extracts and Phytochemicals with Antioxidant Properties against Dyslipidemia and Obesity in the *C. elegans* Model[a]

Vegetable extracts				
		Effects		
Extract	Treatment concentration	Oxidative stress	Dyslipidemia and obesity	ref.
Mulberry fruit anthocyanin extract	100 μg/mL	↑ SOD, GPx, GSH ↓ MDA ↑ MPK-1 ↑ DAF-16, SKN-1, and PMK-1 ↑ Resistance to glucose toxicity and oxidative stress (paraquat) ↑ Lifespan	↓ Lipid content	266
Citrus aurantium ethanol extract	0.25, 0.5, and 1 mg/mL	↓ ROS ↓ MDA ↑ SOD	↓ Triglyceride content ↓ Lipid accumulation	267
Purple pitanga (*Eugenia uniflora*) ethanolic extract	0.76, 1.52, 2.28, 2.28, and 3.8 mg/mL GAE	-	↓ Total lipid ↓ Triglycerides	268
Extracts of *Gardenia jasminoides* fruits and the sclerotia from *Inonotus obliquus*	100 μg/mL	↑ Survival rate	↓ Lipid content	269
Polygonum multiflorum ethyl acetate and butanol extracts	0.5 and 1 mg/mL	↑ SOD, CAT ↓ MDA	↓ Total triglyceride	270
Phytochemicals				
		Effects		
Phytochemicals	Treatment concentration	Oxidative stress	Dyslipidemia and obesity	ref.
Momordica saponins and *Cyclocarya palyurus* polysaccharide beverage	NS	↑ SOD3, DAF-16 ↓ ROS, MDA	↓ Fat accumulation, size, and number of lipid droplets	271
Epigallocatechin-3-gallate (EGCG) and caffeine	EGCG: 0.1 and 0.2 mM Caffeine: 10−30 mM	-	↓Total lipid, triglyceride, and cholesterol content (higher potency than the currently used drug for obesity treatment, orlistat) Combination of compounds was synergistic for lowering of triglycerides	272
Orientin	100 μM	↑ Survival rate of paraquat-exposed worms ↓ ROS ↑ Expression of DAF-16 targets ↑ SOD-3, SKN-1 ↑ Lifespan ↓ aging phenotype ↑ heat and pathogen stress resistance	↓ Fat content and lipid droplet size ↑ *acs-2* fatty acid catabolism gene expression ↑ *fat-1, fat-3,* and *fat-6* lipid synthesis gene expression, ↑ *lipl-4* l lipase gene expression	273
Alkaloids from *Citrus auriantum* L. var. *amara* Engl. flower	0.5 and 1 mg/mL	↑ SOD ↓ ROS, MDA	↓triglycerides, total cholesterol ↓*fat-5, fat-6* and *sbp-1* lipid synthesis gene expression ↓*cebp-2* and *nhr-80* lipid metabolism genes expression ↓*nhr-49* and *mdt-15* lipid catabolism gene expression	274

[a]ROS: reactive oxygen species, MDA: malondialdehyde, GSH: glutathione, DAF-16: orthologue of forkhead box O1 human (FOXO1), SKN-1: orthologue of nuclear factor erythroid 2-related factor 2 (Nrf-2), SOD: superoxide dismutase, GPx: glutathione peroxidase, MPK-1: orthologue of mitogen-activated protein kinase human (1MAPK1), PMK: P38 mitogen-activated protein kinase, *fat:* fatty acid desaturase genes, *acs-2*: acetyl-coenzyme A synthetase, *lipl-4*: lipase 4, NS: not specified.

Alzheimer's disease. Nematode strains employed as a model of this disease express and accumulate human amyloid-β peptide, and when this occurs in body wall muscles, it results in worm paralysis, which can be easily assessed. The other phenotypes, although not that easily evaluated, can also be measured by specific assays.[228−230] As shown in Table 4, strains differ in characteristics, such as the location of amyloid-β peptide expression and the length of the produced peptide.[218] There are also strains expressing fluorophore-tagged amyloid-β peptide.

Concerning Parkinson's disease models, α-synuclein transgenic models are widely used. These models recapitulate a major cellular feature of Parkinson's disease, the presence of Lewy bodies which consist of α-synuclein aggregates.[219] As evidenced in Table 4, these nematode strains differ in the expressed transgene, and as in Alzheimer's models, there are tagged transgene products and different sites of expression by each strain. Noteworthy, movement impairment phenotypes can be easily evaluated; for instance, α-synuclein-induced reduction in the number of body bends can be assessed manually.[219]

Notably, there are also models where nematodes are exposed to agents that induce neurodegenerative-related phenotypes. For instance, treatment with 6-hydroxydopamine (6-OHDA), a dopamine structural analog that leads to oxidative stress and dopaminergic neuron loss, is used to model Parkinson's disease.[231]

As a perspective, the study of antioxidant agents in *C. elegans* models of neurodegeneration could also use omics technologies to view the entire picture. As a matter of fact, lipidomics and metallomics methods have been recently improved in this organism,[232] thus favoring the study of the involvement of lipids (relevant ROS targets) and redox-active metals in both neurodegeneration and neuroprotection in *C. elegans* models.

Among these antioxidant agents, an important issue to consider is their ability to cross the blood−brain barrier (BBB), which is required for treating neurodegenerative diseases. In this regard, agents such as cannabidiol, which has already been reported to cross the BBB,[254] deserve special attention.

Extracts that people can easily access also deserve future studies. For instance, tomato, which is found in almost every country[255] and whose juice (proven agent) is easily obtained,

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could be an option for treatment in countries with drug access problems.

3.3. Dyslipidemia and Obesity. Obesity and dyslipidemia are central public health problems since their global prevalence is currently increasing, and both conditions have a high number of related deaths.[256,257] Obesity and overweight, described as excessive or abnormal fat accumulation, affect more than 2 billion people worldwide and impair health by leading to conditions such as diabetes mellitus, hypertension, and cardiovascular disease.[256,258] Obese patients also usually present serum lipid abnormalities termed dyslipidemia.[259] Dyslipidemia is a group of chronic pathologies characterized by increased cholesterol, triglycerides, or both levels and alterations in related lipoprotein species.[260] Dyslipidemia can be secondary not only to obesity but also to diabetes, hypothyroidism, and an unhealthy lifestyle.[261] Importantly, dyslipidemia is a significant risk factor for atherosclerotic cardiovascular disease and is related to 4 million deaths per year globally.[262] Currently, there are established management guidelines and pharmacotherapy for both obesity and dyslipidemia; however, these strategies are not fully efficient.[263,264] In this context, targeting oxidative stress, which is a relevant component of the pathophysiology of both conditions, could be an option. Oxidative stress participates in obesity and dyslipidemia through mechanisms such as stimulation of adipocyte differentiation and hypertrophy, modulation of hypothalamic signaling which results in reduction of anorexigenic signaling, induction of inflammation (central component of obesity), and cholesterol synthesis enhancement.[265] Notably, some natural antioxidant agents have been observed to exert protective effects against dyslipidemia and obesity characteristics in *C. elegans* (Table 6).

Of these antioxidant agents, there are 4 deserving special future attention: the epigallocatechin-3-gallate (EGCG)−caffeine combination, *Momordica* saponins, the *Cyclocarya palyurus* polysaccharide beverage, orientin, and *Citrus auriantum* alkaloids. Regarding the EGCG−caffeine combination, the observed effects were notable since these agents have a higher potency for lipid reduction than a currently used drug. Moreover, plant sources of both agents, such as *Camelia sinensis* and *Coffea* species, are widely found.

Concerning *Momordica* saponins and the *Cyclocarya palyurus* polysaccharide beverage, it presents a relevant advantage, a pleasant flavor,[271] which may facilitate patients' adherence to treatment.

Regarding orientin and *Citrus auriantum* alkaloids, future research could focus on these agents since, as shown in Table 6, they exert beneficial effects against obesity and dyslipidemia, and some of their molecular targets have already been described.

Finally, it is relevant to mention some aspects of the methods used in this research. Some of these studies use not only normal worms but also a worm high-fat model, which is established by adding a high glucose concentration to the growth media.[271] Other relevant techniques used in these studies are the lipid content assessment by Nile red and oil red O staining. Nile red stains neutral lipids such as triglycerides and cholesterol esters and has excitation and emission maxima of 450−500 and 520 nm, respectively.[275] Some advantages of using this dye are its strong color, negligible interaction with surrounding tissues, and the fact that it is less soluble in solvents than in lipids. Concerning oil red O, it stains triglycerides and lipoproteins in red, and its light absorption maximum is 518 nm. The transparency of nematodes allows oil-red O-stained lipids to be clearly observed.[275]

4. CONCLUSION AND FUTURE PERSPECTIVES

C. elegans is a useful model for screening natural extracts and compounds for its effects against oxidative stress and related pathologies. Research on the antioxidant activity of vegetal extracts and metabolites is extensive, but future studies could focus on antioxidants of vegetal material that is widely found, such as tomatoes, apples, garlic, and green tea. Importantly, antioxidant agents for future studies on neurodegenerative diseases could be selected by function of their previously reported capacity to cross the BBB. As previously mentioned, since the mitochondria is the main source of ROS, studies on antioxidant effects on the function and structure of this organelle could be carried out in this useful model before continuing the preclinical investigation that will lead to phytopharmaceutical development.

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