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Beyond petri dish: small animal models bridge *in vitro* and *in vivo* antioxidant assays

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Abstract

Dietary antioxidants, derived mainly from plant-based foods contribute to health promotion by supporting the body's defense against oxidative stress-related disorders. In vitro assays are widely employed to evaluate the antioxidant capacities of food-derived compounds, providing rapid and cost-effective insights into their radical scavenging and reducing potential. However, these methods do not account for factors such as digestion, absorption, metabolism, and tissue distribution, which determine the physiological relevance of antioxidants. Therefore, in vivo models are essential to complement in vitro findings, enabling a more accurate assessment of bioavailability, mechanisms of action, and health benefits in a biological context. Small animal models provide versatile platforms to bridge this gap, offering genetic tractability, conserved pathways, and cost-effective tools for functional validation of dietary antioxidants. In this review, we summarize the antioxidant defense mechanisms and experimental approaches utilized in zebrafish, *C. elegans*, and fruit fly to investigate the impact of dietary antioxidants. Key outcomes of antioxidative action in these models include the reduction of reactive oxygen species, upregulation of endogenous defense systems, protection of biomacromolecules from oxidative damage, and lifespan extension. Furthermore, this review outlines future directions for utilizing these small animals as translational models in the investigation of food-derived antioxidants.

Keywords: Antioxidants; Zebrafish; *C. elegans*; Fruit fly; Oxidative stress.

1. Introduction

Antioxidants play a critical role in maintaining human health by mitigating oxidative stress, an imbalance between reactive oxygen species (ROS) and the body's antioxidant defences, which is a key contributor to the pathophysiology of chronic diseases, including cardiovascular disorders, neurodegenerative conditions, diabetes, cancer, and premature aging (Pizzino et al., 2017; Chandrasekara et al., 2024).The antioxidant compounds can be enzymatic (e.g., superoxide dismutase(SOD), Catalase(CAT), glutathione peroxidase (GPx) or non-enzymatic (e.g., phenolics, certain vitamins, carotenoids), and maintain redox homeostasis by neutralizing ROS and preventing damage to DNA, proteins, and lipids (Kruk et al., 2022; Senadheera et al., 2023).The consumption of antioxidant-rich foods like fruits and vegetables can be recommended to avoid chronic diseases associated with oxidative stress. Bioactive compounds, which are natural chemicals responsible for antioxidant activity of foods, herbs, mushrooms, and other sources, have gained significant attention for their ability to improve health and help prevent disease beyond the basic roles of macro- and micronutrients. They exhibit diverse biological activities beyond the antioxidant activity, such as anti-inflammatory, antimicrobial, and immunomodulatory effects, making them more important in preventing and managing chronic conditions (Muscolo et al., 2024; Rahaman et al., 2023). For example, polyphenols in fruits and vegetables act as antioxidants with potential in obesity, diabetes,

cardiovascular disease, and cancer management. At the same time, resveratrol in grapes and red wine has demonstrated anticancer effects by inhibiting tumour cell growth and proliferation. Recent evidence supports this by showing an inverse correlation between the blood concentration of antioxidants like vitamins C and E and non-communicable disease rates. The glucose metabolism and blood pressure regulation, crucial in controlling hypertension and diabetes, are done by bioactive peptides derived from natural sources (Farhan and Rizvi, 2023; Ciupei et al., 2024). On the other hand, phytochemicals in herbs and spices show anti-obesity and lipid-lowering effects. This is evidenced by recent studies that further highlight their broad potential: mushrooms like *Pleurotus ferulae* and *Chroogomphus rutilus* reduce adiposity, improve lipid profiles, and exhibit antioxidant and antitumor effects; anthocyanin-rich berries (*Vaccinium* spp.) protect against inflammation and cancer; and yacon flour reduces colorectal cancer–related inflammation in animal models (Jeayeng et al., 2024).

Additionally, some marine microalgae, such as *Chlorella*, improve exercise performance through antioxidant and metabolic activities, while medicinal plants like *Momordica charantia* and *Persea americana* support glucose regulation and weight management (Lorenzo et al., 2023; Laczkó-Zöld et al., 2024). Nevertheless, compounds such as capsaicin from chilli peppers enhance thermogenesis, gut health, and antioxidant status, and bio actives like ω-3 fatty acids, sulforaphane, and bromelain have shown promise as adjuvants in breast cancer prevention and treatment. These examples highlight the varied roles in health and wellness, underscoring the need for more clinical research to confirm safety, efficacy, and long-term benefits. Therefore, bioactive compounds from natural sources have drawn increasing attention for their potential to promote health and prevent disease beyond basic nutritional functions (Corral-Guerrero et al., 2025).

The diversity of antioxidant assessments to evaluate the alleviating potential of oxidative stress from different sources is very important to understand. Researchers are looking for new effective methods to assess antioxidant capacity due to the difficulties of reliably predicting human physiological responses using traditional in vitro assays and mammalian models, which are usually applied in biomedical research, drug testing, and toxicity assessments (Shahidi and Danielski, 2024; Gulcin, 2025). The static cell cultures, which are also a kind of *in vitro* system, offer high capability of throughput but make the cellular environment oversimplified, which makes it hard to replicate critical dynamic processes like fluid flow, cellular interactions, and the complex metabolism and bioavailability of compounds that occur *in vivo* (Ryoo et al., 2024). Furthermore, their translational relevance is often limited by variability in environmental conditions, such as pH and oxygen levels, which can drastically affect outcomes. In case of oxidative stress assessment through mammalian models makes more beneficial with having biologically complex system their use is obstructed by ethical concerns, high costs, extended study durations, and crucial species differences; for example, transgenic mouse models can have significant genetic divergences that fail to replicate human disease mechanisms accurately (Liu et al., 2025). Additionally, some of the limitations of specific assays, such as the mouse aortic ring assay applied to angiogenesis, are exacerbated by their dependence on stressful surgical procedures and poor reproducibility due to variability in assay conditions and readouts. These shortcomings underscore the need to develop more predictive, human-relevant models, such as organ-on-chip technologies, to better mimic human physiology and pathology (Baker et al., 2012; Razmi et al., 2025).

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As a powerful and ethically favourable alternative for conventional methods in measuring oxidative stress, attention towards small model organisms like zebrafish (*Danio rerio*), *Caenorhabditis elegans*, and *Drosophila melanogaster* has become indispensable in antioxidant research. Their advantages are multifaceted: high genetic tractability, remarkably short life cycles, low cost, and a high degree of physiological conservation in fundamental redox and stress-response pathways with humans (Zhang et al., 2024a). These characteristics allow for high-throughput screening of oxidative stress and natural bioactive antioxidants, which are increasingly prioritized over synthetic options. Compared to the traditional *in vitro* systems, these small models provide a whole-organism context while mimicking complex cellular environments, including bioavailability and metabolism, to assess antioxidant efficacy from molecular activity to systemic health outcomes such as improved lifespan or stress resistance. Therefore, reviewing the applications of these small models is critical for rapidly validating the therapeutic potential of antioxidants derived from diverse natural sources, such as plant extracts, microalgae, and sea cucumbers, and for advancing their use in food preservation, nutraceuticals, and cosmetic applications (Zhang et al., 2024b).

2. Molecular and cellular mechanisms of antioxidant defense

Antioxidant defence mechanisms are fundamental to cellular homeostasis, protecting against oxidative stress caused by reactive oxygen species (ROS). The Nrf2 signalling pathway primarily orchestrates this defence (Verma et al., 2023). Upon activation by oxidative stress, Nrf2 transcription factors move towards the nucleus and bind to antioxidant response elements (AREs), inducing the transcription of major antioxidant enzymes such as CAT, SOD, and GPx (Ngo and Duennwald, 2022; Hammad et al., 2023). This system is further fine-tuned through post-translational modifications, allowing cells to rapidly adjust their defences in response to fluctuating ROS levels. These enzymes are vital in vascular biology and manipulating

Nrf2 as a promising therapeutic strategy for cardiovascular diseases, where their decreased activity is associated with endothelial dysfunction and inflammation (Liu et al., 2025).

The generation of ROS is a normal physiological process, but oxidative stress occurs when its production overwhelms the body's antioxidant capabilities. However, conditions like chronic hyperglycemia, hypoxia, and substance abuse exacerbate the imbalance of ROS generation, leading to significant cellular damage through lipid peroxidation, DNA damage, and apoptosis and on the other hand, contributing to the pathogenesis of some neurodegenerative disorders like Alzheimer's disease, cardiovascular complications via endothelial dysfunction, and metabolic syndromes. Furthermore, oxidative stress also significantly affects reproductive health, which presents a significant challenge to in vitro fertilization, where mitochondrial ROS production can damage oocytes and embryos (González et al., 2023; Bhatti et al., 2022).

To assess oxidative damage, specific biomarkers such as malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) to measure Lipid peroxidation, 8-hydroxy-2′-deoxyguanosine (8-OHdG) to measure cellular DNA damage, and protein oxidation by protein carbonyls are utilized (AbuArrah et al.,2021). The analysis of these biomarkers provides critical insights into disease severity, as seen in conditions like COVID-19 and cancer, and helps elucidate the underlying pathological mechanisms. In addition to the application in patient diagnosis and stratification, the monitoring of these biomarkers also holds therapeutic promise for guiding interventions, such as the use of dietary polyphenols like resveratrol, which can enhance antioxidant defences through both Nrf2 activation and direct post-translational modifications of protective enzymes (Jain, 2010).

2.1. The zebrafish (Danio rerio) as a model for antioxidant and oxidative stress research

The zebrafish (*Danio rerio*) has emerged as a preeminent model organism for investigating antioxidant mechanisms and oxidative stress, largely due to its unique combination of biological, genetic, and experimental advantages. A major strength is the optical transparency of its embryos and larvae, which permits direct, high-resolution, real-time imaging of physiological and pathological processes *in vivo* without invasive procedures (Srivastava et al., 2025).This feature is complemented by a high degree of genetic tractability; advanced genome-editing technologies like TALENs and CRISPR, along with a wide array of stable transgenic lines expressing fluorescent reporters, facilitate detailed mechanistic studies (Du et al., 2025). Furthermore, the zebrafish genome is fully sequenced and exhibits remarkable conservation with humans, with approximately 80% of human genes having a counterpart (Tasnim et al., 2024) .This is particularly true for genes governing oxidation, lipid metabolism, and inflammation, ensuring that findings are often translatable to mammalian systems (Teame et al., 2019).

These attributes make zebrafish an unparalleled platform for toxicological and pharmacological research, allowing for the real-time observation of oxidative stress responses during their rapid embryonic development (Zhang et al., 2021). The model has been effectively used to demonstrate the physiological implications of oxidative stress, such as acute sensitivity to ROS. Consequently, numerous studies have utilized zebrafish to screen and evaluate the efficacy of various antioxidants. For instance, quercetin nanocrystals, tamarind shell extract, and *Cassia fistula* stem bark have all been shown to mitigate hydrogen peroxide-induced oxidative stress, demonstrating significant reductions in ROS production and protective roles against cellular damage (Li et al., 2023b; Wang et al., 2023a).

At the molecular level, zebrafish research has elucidated key pathways like the Nrf2-Keap1 signaling cascade, which regulates the expression of antioxidant genes in a manner that parallels mechanisms in mammals (Nguyen et al., 2018). Studies consistently highlight the activation of critical antioxidant enzymes, including CAT and GPx, as essential for maintaining redox homeostasis (Wang et al., 2023b). The use of fluorescent probes has further enabled the visualization of metabolic dynamics, such as cysteine metabolism, under oxidative stress in living organisms (Yu et al., 2025). This utility extends to environmental toxicology, where zebrafish have been instrumental in linking pollutant exposure (e.g., bisphenol A) to oxidative damage and in documenting the protective effects of potential therapeutic compounds like antioxidant peptides (Guru and Arockiaraj, 2023).Thus, the combined attributes of transparency, genetic manipulability, and physiological homology make the zebrafish an indispensable platform for advancing both basic and therapeutic research into redox biology. Figure 1. Different antioxidant detection methods using zebrafish models discussed in this review. The figure summarizes *in vivo*, *in vitro*, and molecular approaches that have been applied in zebrafish for evaluating antioxidant capacity and oxidative stress mechanisms. Figure 2. Different antioxidant detection methods using zebrafish models.

2.2. Zebrafish in oxidative stress toxicology

One of the most significant applications of the zebrafish model lies in toxicological research, where it is extensively employed to evaluate the oxidative stress potential of environmental contaminants and to elucidate underlying molecular pathways. For instance, exposure to perfluorooctane sulfonate (PFOS) induces a concentration-dependent increase in ROS and markedly upregulates the activity of key antioxidant enzymes—SOD, CAT, and GPx—as a cellular defense mechanism (Shi and Zhou, 2010). The primary mechanism for this response involves the Nrf2 pathway, a central regulator of antioxidant defenses. Activation of Nrf2 mitigated PFOS-induced damage, whereas its knockdown exacerbated oxidative stress (Shi and Zhou, 2010).

Similarly, nanotoxicology studies have shown that titanium dioxide nanoparticles (NM-TiO_2), particularly in anatase-rich forms, exhibit significantly enhanced toxicity under simulated solar radiation due to elevated ROS generation, resulting in oxidative tissue damage (Faria et al., 2014). These findings emphasize the zebrafish model's value in revealing how pollutants disrupt oxidative homeostasis and in identifying the protective mechanisms involved.

The zebrafish is also well suited for experimental setups designed to mimic oxidative stress conditions. For example, exposure to pro-oxidants such as tert-butyl hydroperoxide (t-BHP) allows researchers to simulate oxidative stress in vivo (Li et al., 2023a). In one study, tamarind shell extract was shown to protect zebrafish against t-BHP–induced oxidative damage, confirming its antioxidant potential (Li et al., 2023a). Likewise, carnosine has demonstrated protective effects against titanium dioxide–induced oxidative stress in zebrafish embryos, further supporting the model's utility for drug discovery and antioxidant screening (Caruso et al., 2023).

Moreover, the genetic manipulability of zebrafish—particularly through CRISPR-based approaches—enhances its role in dissecting molecular mechanisms of oxidative stress. Loss- and gain-of-function mutants of the Nrf2a gene have been used to clarify how this pathway regulates antioxidant gene expression and mediates

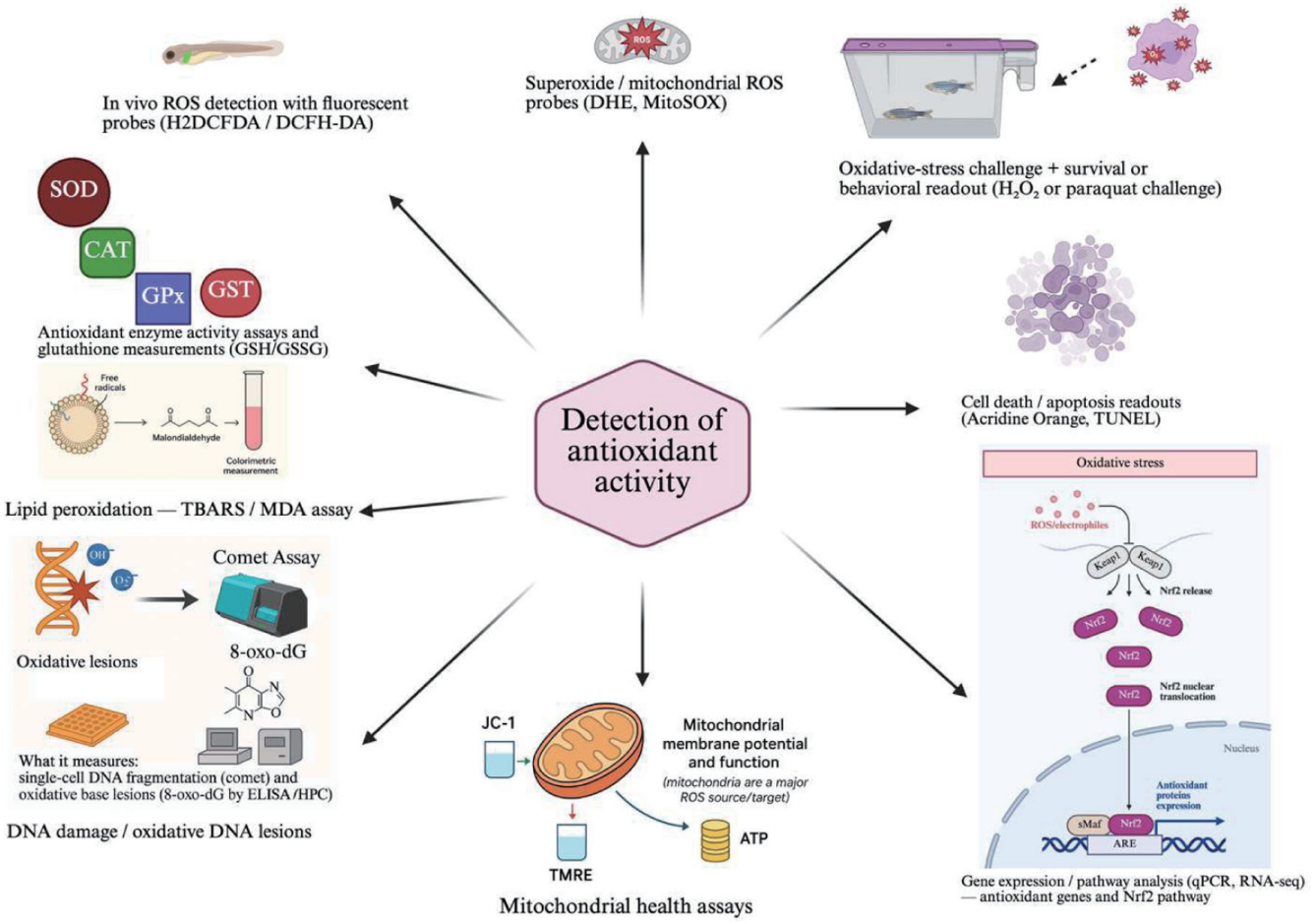

Figure 1. Different antioxidant detection methods using zebrafish models.

toxicity responses (Mills et al., 2019). These genetic tools also allow researchers to assess how natural compounds influence oxidative stress responses. For example, soy-derived equol has been investigated in zebrafish larvae, revealing both Nrf2-dependent and independent mechanisms of antioxidant protection (Watanabe et al., 2022).

3. Screening therapeutic antioxidants and evaluating bioactive compounds

Beyond toxicology, the zebrafish has emerged as an invaluable model for screening and evaluating the efficacy of natural and synthetic antioxidants, offering critical functional and safety data. Research on sulfated polysaccharides from the brown alga *Sargassum tenerrimum* demonstrated potent radical-scavenging activity in vitro and a strong cytoprotective effect in vivo, significantly decreasing H_2O_2-induced ROS production and cell death in embryos while improving survival and heart rates (Raguraman et al., 2019). The model also enables insights into the therapeutic potential of compounds for complex disorders. For instance, nicotine metabolites were found to alleviate scopolamine-induced anxiety and memory deficits in zebrafish, with their effects attributed to robust antioxidant properties that enhanced the activity of key antioxidant enzymes and glutathione levels while reducing lipid peroxidation (Popovici et al., 2025).

Importantly, the zebrafish model is crucial for safety assessment, as high antioxidant capacity in vitro does not necessarily translate to safety in vivo. This was illustrated in a study of native Australian fruits, where Kakadu plum extract—with high antioxidant activity—was among the least toxic, whereas Muntries extract—with lower antioxidant metrics—proved the most toxic, causing significant mortality and hatching delays (Ali et al., 2022). Such findings underscore the importance of zebrafish in validating both the efficacy and the safety of potential antioxidant therapies.

Focusing on specific natural antioxidants, several studies have identified effective food-derived phytochemicals. Compounds such as curcumin and diallyl trisulfide have shown significant protective effects against oxidative stress in zebrafish larvae (Watanabe et al., 2022). Similarly, chlorogenic acid supplementation demonstrated benefits for exposed zebrafish embryos, highlighting the therapeutic promise of dietary antioxidants (Chiu et al., 2020). Moreover, the antioxidant Riboceine successfully rescued craniofacial defects in zebrafish exposed to auranofin, showcasing the practical applications of antioxidant research in developmental biology (Leask et al., 2021).

Zebrafish models also support high-throughput screening of antioxidant compounds, enabling the identification of those with substantial protective effects against oxidative stress. For example, fucoidan from *Undaria pinnatifida* exhibited protective properties

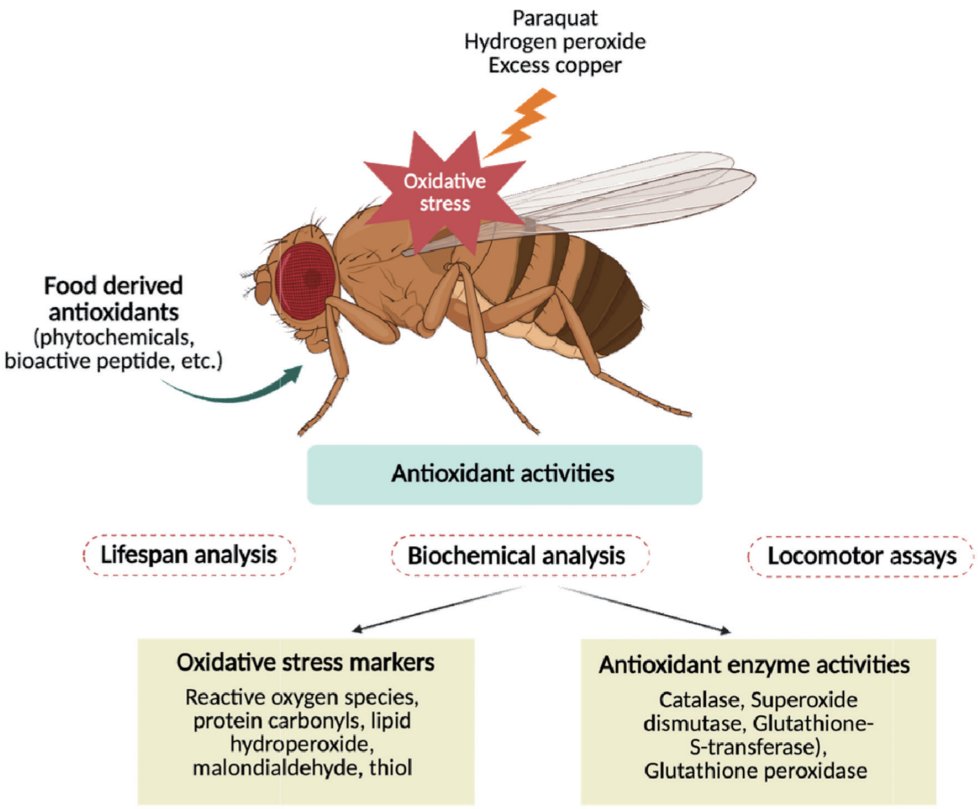

Figure 2. D. melanogaster as a small in vivo model to study antioxidant activities of food derived antioxidants.

in AAPH-induced oxidative stress assays (Oh et al., 2020). Additionally, research has revealed that phosvitin, a protein isolated from zebrafish, possesses potent antioxidant activity, suggesting that the amino acid composition of zebrafish proteins contributes significantly to their capacity to mitigate oxidative damage (Hu et al., 2015). Collectively, these studies demonstrate how zebrafish-based research, combined with modern genetic tools, can elucidate the mechanisms through which natural compounds exert their antioxidative effects.

4. Integrative omics for antioxidant research in zebrafish

The application of integrative omics approaches, such as transcriptomics, proteomics, and metabolomics, in zebrafish (*Danio rerio*) research underscores the utility of this model organism in evaluating the antioxidant potential of natural sources. Zebrafish are increasingly utilized in studies assessing oxidative stress due to their genetic similarities to humans and their transparent embryos, which permit real-time observation of biological processes.A significant area of research involves the use of natural extracts to mitigate oxidative stress. For example, the antioxidant effects of Moringa oleifera leaf extract have been demonstrated in zebrafish exposed to imidacloprid toxicity. The extract has been shown to enhance levels of antioxidant enzymes, thereby alleviating the harmful effects associated with oxidative damage in liver tissues (Yadav et al., 2020). Moreover, Moringa compounds, which are rich in essential amino acids, have been indicated to promote protein synthesis and mitigate oxidative damage, further highlighting their pharmacological relevance (Yadav et al., 2020).In addition, the effects of various antioxidants, including nanoparticles such as selenium (Se) and zinc oxide (ZnO), on zebrafish growth and modulation of oxidative stress have been explored. Research indicates that the incorporation of these nanoparticles significantly enhances growth performance and modulates gene expression related to oxidative stress, indicating their potential as nutraceuticals in fish feeds aimed at improving aquaculture outcomes (Fasil et al., 2021). These findings suggest that integrative omics can elucidate the mechanisms by which natural antioxidants operate at molecular and cellular levels, revealing pathways implicated in growth and stress responses.Natural sources of antioxidants extend beyond traditional medicinal plants. Marine resources, such as astaxanthin, have emerged as potent antioxidants. Carotenoids like astaxanthin are recognized for their role in mitigating oxidative stress and enhancing immune responses in fish, thus improving the health and resilience of fish stocks under farming conditions (Akhmedzhanova et al., 2022; Córdova et al., 2018). In this context, zebrafish serve as an optimal model for studying the effects of such antioxidants, allowing for precise metabolic profiling and comparative studies of antioxidant efficacy under various environmental conditions.Furthermore, the role of phenolic compounds from diverse natural sources in preserving the quality of fish has been investigated. Research indicates that extracts rich in phenolics provide antioxidant activity comparable to synthetic alternatives, thus improving oxidative stability in seafood products (Pezeshk et al., 2015). The assessment of these natural antioxidants through omics approaches could lead to a deeper understanding of their mechanisms and efficacy in real-world scenarios, particularly within the aquaculture industry (Taşbozan and Erbaş, 2023).

4.1. As a model for diet-induced oxidative stress research

This model organism's favorable characteristics, such as its genetic and physiological similarity to higher vertebrates, allow researchers to effectively test dietary components for their antioxidant capacity and metabolic impacts. Recent studies underscore the role of specific micronutrients in boosting the antioxidant defenses of zebrafish. For instance, Fasil et al. demonstrate that the supplementation of zinc oxide (ZnO) and selenium significantly enhances growth performance by modulating oxidative stress and influencing gene expression relevant to growth, such as growth hormone (GH) and insulin-like growth factor 1 (IGF-1) (Fasil et al., 2021). The interplay between these nutrients reinforces the synergistic effects of antioxidants in promoting overall fish health. Further investigations have illustrated how external environmental factors, such as exposure to contaminants, can adversely affect the oxidative status of aquatic organisms. For example, Velanganni et al. documented that exposure to benzophenone-3, a common water pollutant, triggered oxidative stress in zebrafish, evidenced by altered antioxidant enzyme activities and increased lipid peroxidation markers (Velanganni et al., 2021). Such environmental stressors highlight the necessity for dietary interventions that enhance antioxidant capacities, as seen in the comparative analyses of synthetic versus natural antioxidants in fish diets conducted by Pereira et al. They found that natural sources, particularly from vegetables like tomatoes, exhibit promising antioxidant potential under both standard and stress-challenged conditions (Pereira et al., 2022).Moreover, various dietary proteins have been explored for their bioactive peptide content, contributing to antioxidant activities. The peptide VY6 derived from β-lactoglobulin was shown to modify lipid metabolism in zebrafish, leading to significant reductions in liver triglycerides and free cholesterol while enhancing HDL levels (Mohammed-Geba et al., 2016). This suggests a pathway by which dietary proteins can be strategically utilized to ameliorate lipid-related oxidative stress in fish.Furthermore, antioxidants sourced from natural plants and microorganisms are garnering attention for their application in fish diets. The study by Vargas-Sánchez et al. highlights the potential of propolis extract as a natural antioxidant, supporting the idea that a diet enriched with natural antioxidants can enhance the oxidative stability of fish products during storage (Vargas-Sánchez et al., 2019). This aligns with the broader literature emphasizing the extraction and application of natural antioxidants from various sources, which, according to Xu et al., are integral in mitigating oxidative stress effects at molecular levels and promoting overall health (Xu et al., 2017).

4.2. Drosophila melanogaster (fruit fly)

Drosophila melanogaster, also known as fruit fly, has emerged as a powerful *in vivo* model for nutritional and biomedical research due to its genetic tractability, short lifespan (average three months at 25 °C), cost effectiveness, and conserved molecular pathways involved in oxidative stress responses (Victor Atoki et al., 2025). It is an economical choice because of its rapid reproduction (30–50 eggs per day), short generation time (around ten days at 25 °C), and minimal maintenance cost. For decades, *D. melanogaster* has served as a highly valuable animal model for investigating genetics, evolutionary processes, and developmental biology. Although *D. melanogaster* is evolutionarily distant from humans, many aspects of its development, physiology, biology, and metabolism closely resemble those of mammals (Lopez-Ortiz et al., 2023). In particular, recent studies highlight parallels in metabolic regulation, including insulin signaling, nutrient sensing, and energy homeostasis, which are relevant to metabolic disorders such as diabetes and obesity (Mattila and Hietakangas, 2017). Recently, fruit flies are being increasingly used in antioxidant studies since flies share homologous antioxidant defense mechanisms with mammals, including SOD, CAT, and glutathione (GSH)-based systems, making them biologically relevant for evaluating antioxidant interventions (Yi et al., 2024). Furthermore, dietary compounds can be readily incorporated into fly food, enabling controlled studies of dose-dependent effects on stress resistance, longevity, and physiological health.

Previous studies have established *D. melanogaster* as a suitable model for antioxidant research on food-derived bioactives (Lopez-Ortiz et al., 2023). Oxidative stress is commonly induced in flies using agents such as paraquat, hydrogen peroxide (H_2O_2), or excess copper, providing a consistent framework to evaluate stress resistance and survival (Demir et al., 2022). Experimental outcomes are typically assessed through lifespan analysis, locomotor assays such as negative geotaxis, and biochemical measurements of oxidative stress markers, including reactive oxygen species (ROS), protein carbonyls, lipid hydroperoxides, malondialdehydes (MDA), and thiol content, as well as antioxidant enzyme activities such as CAT, SOD, glutathione-S-transferase (GST), and GPx as shown in Figure 1. Furthermore, disease models in *D. melanogaster*, including α-synuclein–based Parkinson's disease models, exhibit elevated oxidative stress and motor impairments, making them particularly valuable for testing antioxidant interventions (Aryal and Lee, 2019). Overall, *D. melanogaster* models are widely applied to investigate the antioxidant potential of dietary phytochemicals and bioactive peptides, which are discussed in the following sections (Table 1).

5. Plant-based antioxidants and oxidative stress modulation

Phytochemicals are naturally occurring bioactive compounds present in fruits, vegetables, grains, legumes, and other plant-based foods, where they contribute to health promotion through their antioxidant and protective properties. These compounds, including phenolics, carotenoids, and alkaloids, can neutralize ROS, chelate transition metals, and stimulate the body's endogenous antioxidant defense systems. A growing body of evidence demonstrates that dietary phytochemicals can extend lifespan, enhance stress resistance, and improve antioxidant capacity in fruit flies, offering insights relevant to human health. Several studies highlight the role of individual compounds and plant extracts in modulating oxidative stress in *D. melanogaster*. For example, Golubev et al. (2022) demonstrated that *Lonicera pallasii* (honeysuckle) extract and its major anthocyanin, cyanidin-3-O-glucoside, modestly increased lifespan and stress resistance while improving intestinal barrier integrity, effects linked to Sirt6 activation and regulation of pro- and anti-longevity genes (*Hif1* and *Keap1*). Together, these findings suggest that phytochemicals can promote longevity and health span through antioxidant and gene-modulatory mechanisms.

Other investigations have focused on plant extracts rich in diverse phytochemicals. *Mangifera indica* cold aqueous leaf extract enhanced fly survival and increased activities of GST and CAT as well as thiol content, although effects were dose-dependent, emphasizing the importance of dose optimization (Alexander et al., 2019). In addition, *Astragalus membranaceus* extract and its bioactive compounds improved oxidative stress resistance by enhancing survival under H_2O_2 challenge, lowering ROS levels, increasing antioxidant enzyme activity (SOD, CAT), and upregulat-

Table 1. Summary of the strengths, limitations, and translational value of zebrafish, fruit fly (*Drosophila melanogaster*), and *Caenorhabditis elegans* in antioxidant research

Model Organism	Key Strengths	Primary Limitations	Translational Value	References
Zebrafish (*Danio rerio*)	High genetic and physiological similarity to humans (vertebrate model). Transparent embryos enabling real-time, live imaging of developmental and pathological processes. Rapid development and high fecundity. Well-suited for high-throughput genetic and drug screening. High conservation of immune and metabolic pathways.	Limited complexity of some organ systems compared to mammals. High lethality in severe genetic mutations. Differences in drug metabolism and anatomy. Limited genetic background diversity in some strains. Not ideal for long-term chronic studies due to lifespan. Limited studies on complex behaviors and mechanisms.	Highly valuable for drug discovery, toxicology, and safety evaluations. Excellent for modeling human diseases, particularly neurodegenerative, metabolic, and inflammatory conditions. Effective for studying developmental processes and *in vivo* oxidative stress dynamics.	Ali et al., 2022; Amen et al., 2020; Quelle-Regaldie, et al., 2023; Shreya et al., 2020
Fruit Fly (*Drosophila melanogaster*)	Extremely short life cycle and rapid generation time. Vast array of well-established, powerful genetic tools for manipulation. Low cost and ease of maintenance. Well-characterized genome. Suitable for high-throughput screening.	Limited physiological and anatomical similarity to humans (invertebrate). Less relevance to complex mammalian systems (e.g., adaptive immunity, complex organ structures). Differences in metabolic pathways. Shorter lifespan can limit long-term studies.	Ideal for initial screening of compounds and for fundamental genetic studies. Provides crucial insights into the genetic basis of aging, oxidative stress mechanisms, and developmental biology. Strong model for gene-environment interactions.	Ajagun-Ogunleye and Ebuehi, 2020; Hamidu et al., 2022; Somegowda et al., 2021
Caenorhabditis elegans (*C. elegans*)	Simple, well-mapped nervous system and genetics. Transparent body allows for easy observation of cellular processes. Very short lifespan and rapid reproduction are ideal for high-throughput longevity and anti-aging studies. Low maintenance cost. Highly conserved genetic pathways.	Extremely simple anatomy lacks complex organ systems (e.g., no heart, liver, adaptive immune system). Limited relevance to vertebrate physiology and complex human diseases. Short lifespan may not model chronic conditions accurately. Limited behavioral complexity.	Exceptional model for screening antioxidants, anti-aging compounds, and neuroprotective agents. Unparalleled for understanding fundamental cellular mechanisms like apoptosis, stress response, and aging. High value in mechanistic studies of oxidative stress and lifespan extension.	de Araújo, 2025; Ayoub et al., 2024; von Mikecz, 2023; Roxo et al., 2020

ing related genes (Sod1, Cat, CncC) (Dai et al., 2024). Curcumin supplementation significantly extended lifespan in male flies, with the effect reversed by a SOD inhibitor, suggesting that curcumin acts through SOD-dependent pathways (Suckow and Suckow, 2006). Likewise, flavonoids extracted from *Epimedium pubescens*, including icariin and epimedins A–C, showed strong radical-scavenging activity and boosted antioxidant enzyme activities (CAT and GSH-Px) in both sexes, reinforcing their potential as natural antioxidants (Yang et al., 2020).

One prominent area of research focuses on how various plant extracts modulate antioxidant enzyme activity and reduce oxidative stress in *Drosophila melanogaster*. For instance, selenium-enriched *Chrysanthemum morifolium* has been shown to significantly influence lifespan and upregulate key antioxidant enzymes, including superoxide dismutase (SOD) and catalase, both of which play crucial roles in mitigating oxidative stress (Feng et al., 2022). Similarly, *Spirulina platensis* extract has been demonstrated to enhance overall antioxidant levels and decrease oxidative damage in fruit flies exposed to toxic compounds, further supporting its protective role (Salim et al., 2019). Collectively, these findings suggest that such natural sources may serve as promising anti-aging and neuroprotective agents.

Research has also investigated the effects of individual dietary components on oxidative stress regulation. For example, phlorizin, a bioactive compound from apples, was reported to increase both SOD and catalase activity in *Drosophila*, strengthening the organism's defenses against reactive oxygen species (ROS) (Wang et al., 2023b). In a similar vein, dietary supplementation with chili pepper extract produced a concentration-dependent extension of lifespan in fruit flies, suggesting that such extracts influence metabolic and stress-response pathways that govern longevity (Semaniuk et al., 2022a).

The implications of these findings are particularly relevant to neurodegenerative disease research, especially Parkinson's disease (PD). In a *Drosophila* PD model involving ubiquitin C-terminal hydrolase (dUCH) knockdown, antioxidants such as curcumin have been found to alleviate PD-like symptoms by reducing oxidative stress (Nguyen et al., 2018). Likewise, natural antioxidants from *Portulaca oleracea* have shown neuroprotective effects in the same model, underscoring their potential as therapeutic candidates for neurodegenerative conditions driven by oxidative damage (Huynh et al., 2019).

In addition to these physiological outcomes, recent studies have shed light on the genetic mechanisms underlying antioxidant responses in *Drosophila*. Pathways involving transcription factors such as FOXO and Nrf2 play central roles in regulating antioxidant enzyme expression in response to dietary antioxidants (Semaniuk et al., 2022b). A deeper understanding of these molecular mechanisms not only supports the effectiveness of plant-derived antioxidants but also lays the groundwork for developing strategies to harness these natural compounds for human health benefits.

More recent studies have expanded the scope of phytochemical testing in *D. melanogaster*. A proanthocyanidin-rich fraction from *Tamarindus indica* improved lifespan, emergence rate, and

antioxidant enzyme activities while reducing acetylcholinesterase and caspase-3/9 activities, indicating both antioxidant and neuroprotective effects (Jaafaru et al., 2024). Similarly, supplementation with *Artemisia argyi* extract significantly prolonged lifespan, improved climbing ability, and increased tolerance to oxidative stress while modulating key antioxidant enzymes and reducing MDA levels (Yang et al., 2024). Apple-derived phlorizin also exhibited strong antioxidant and anti-aging properties, including lifespan extension, improved locomotor performance, upregulation of *Nrf2/cnc* and related genes, and downregulation of *methuselah*. Computational analysis further suggested that phlorizin functions as a Nrf2 activator, linking its effects to endogenous stress response pathways (Wang et al., 2019). Collectively, these findings underscore the utility of *D. melanogaster* as a model for studying the antioxidant and anti-aging effects of phytochemicals and provide mechanistic insights with translational potential.

5.1. Bioactive peptides

Bioactive peptides, short protein fragments released from dietary proteins, have emerged as important natural antioxidants with health-promoting effects that extend beyond basic nutrition. Their antioxidant activity is attributed to free radical scavenging, transition metal chelation, and regulation of endogenous defense systems. Owing to these properties, *Drosophila melanogaster* has been increasingly employed as an in vivo model to investigate the antioxidant and anti-aging effects of food-derived peptides.

Several studies have demonstrated the ability of dietary peptides to enhance stress resistance and prolong lifespan in *D. melanogaster*. Chen et al. (2020) reported that crimson snapper scale peptides significantly extended lifespan in a dose-dependent manner, reduced MDA and protein carbonylation levels, and enhanced antioxidant enzyme activities (thiol modified-SOD and CAT), while upregulating antioxidant-related genes (*SOD1*, *SOD2*, *CAT*). Similarly, supplementation with rice protein hydrolysates (0.2 and 3.2%) increased lifespan, boosted antioxidant enzyme activities (SOD, Manganese-SOD, CAT), and modulated key signaling pathways, including Nrf2/Keap1, TOR/S6K, and the longevity gene *methuselah* (Yue et al., 2021). Casein supplementation has also been shown to counteract oxidative stress: Sadiq et al. (2023) demonstrated that 1% casein improved survival, restored GSH, thiols, and protein levels, and normalized oxidative stress biomarkers in flies, potentially through Keap1/Nrf2 pathway regulation.

More recently, *Lateolabrax japonicus* peptides (LPH) have been evaluated for their antioxidant potential in flies subjected to H_2O_2-induced oxidative stress. LPH supplementation extended lifespan, reduced ROS and MDA levels, enhanced antioxidant enzyme activities (SOD, CAT, GSH-Px), and preserved intestinal structure by regulating stem cell proliferation. Mechanistically, LPH activated Nrf2-related genes, downregulated mTOR, and modulated gut microbiota composition, suggesting a multifaceted mechanism of action (Chen et al., 2025). Collectively, these findings highlight the strong potential of food-derived bioactive peptides as functional ingredients for enhancing oxidative stress resilience and delaying aging, with *D. melanogaster* serving as a powerful model for mechanistic insight.

6. Integrative omics of antioxidants in *Drosophila*

Integrative omics studies using *Drosophila melanogaster* have become a powerful approach for assessing the antioxidant potential of natural sources, offering valuable insights into the identification and quantification of bioactive compounds. The advantages of using *Drosophila* include their short life cycle and well-characterized genetics, which enable rapid evaluation of the physiological effects of natural antioxidants. For example, curcumin tested in *Drosophila* has demonstrated significant pharmacological effects linked to its antioxidant activity, underscoring the relevance of this model for in vivo efficacy studies (Rumata et al., 2023). Such approaches also shed light on the role of diet in health and longevity, as shown by studies investigating the impact of antioxidant-rich diets on lifespan extension in fruit flies (Liedo et al., 2012).

The mechanisms by which natural antioxidants mitigate oxidative stress are also being actively explored in fruit fly models. Research indicates that *Drosophila* can serve as experimental platforms for evaluating the therapeutic potential of diverse antioxidant sources, including mushrooms, which are rich in bioactive compounds with strong antioxidant capacity (Sánchez et al., 2015). Similar findings in related species, such as the Mexican fruit fly (*Anastrepha ludens*), reveal a positive correlation between consumption of antioxidant-rich nutraceutical compounds and improvements in longevity and overall health (Sánchez et al., 2015).

The integration of advanced omics technologies—such as metabolomics and transcriptomics—further enhances understanding of the biochemical pathways influenced by antioxidants. Multi-omics approaches reveal specific metabolic and gene-expression shifts in response to antioxidant supplementation, as demonstrated in studies examining fruit fly responses to different antioxidant treatments (Lazzari et al., 2020). These integrative data analyses provide a holistic view of the interactions between metabolic pathways and antioxidant compounds, facilitating the identification of health-promoting mechanisms (Rodrigues et al., 2024).

Additionally, comparative studies of antioxidant activity among different food sources have highlighted variations in bioactive compound profiles, which are shaped by both genetic and environmental factors. Such research underscores the value of *Drosophila* as a model not only for biomedical applications but also for agricultural and nutritional studies aimed at improving food quality and promoting health (Ismail et al., 2023). Together, the synergy between integrative omics and fruit fly models opens new avenues for antioxidant research, functional food development, and translational applications for human health.

7. Oxidative stress and dietary interventions

The use of *Drosophila melanogaster* in dietary intervention research has proven highly effective for evaluating the antioxidant properties of various natural sources, particularly fruits and their derivatives. This organism, commonly known as the fruit fly, serves as a robust model due to its genetic similarity to humans and its short life cycle, which allows for rapid investigation of dietary effects on health and longevity (Hof-Michel et al., 2025; Staats et al., 2018).

A key focus in this field is identifying beneficial fruit-derived compounds with potent antioxidant properties. Polyphenols, carotenoids, and other bioactive antioxidants from fruits have been shown to improve health outcomes in *Drosophila* models. For example, *Spirulina platensis* extracts, rich in antioxidants, have been demonstrated to mitigate oxidative stress, enhance resistance to $FeSO_4$-induced toxicity, reduce mortality rates, and improve locomotor function in fruit flies (Salim et al., 2019). Similarly, diets high in antioxidants are positively associated with extended lifes-

pan and improved metabolic profiles in *Drosophila* (Jo and Imm, 2017).

Phenolic compounds, particularly abundant in cherries, berries, and other fruits, are of notable interest due to their ability to lower oxidative stress markers and reduce the risk of chronic diseases such as cardiovascular disorders (Zujko et al., 2022). The concept of total antioxidant capacity (TAC) has emerged as a valuable metric for evaluating diet quality, with studies linking high-TAC diets to reduced oxidative damage and enhanced overall health metrics in *Drosophila* models (Xu et al., 2017; Frakchi et al., 2024; Mancini et al., 2017).

In addition, research highlights that specific dietary components, such as sucrose, can modulate the oxidative defense system in *Drosophila*, suggesting that dietary moderation plays a significant role in influencing oxidative stress responses, tissue damage, and longevity (Sánchez et al., 2015). The inclusion of natural antioxidants from açaí berries has also been associated with positive health outcomes, reinforcing their potential as functional food components in targeted dietary interventions (Strilbytska et al., 2022).

Furthermore, studies integrating *Drosophila* models into nutrigenomics research emphasize the importance of understanding how dietary interventions interact with genetic factors to optimize health outcomes (Ferreira et al., 2016). This area of research holds promise for guiding policymakers and nutrition experts in developing dietary guidelines that strategically leverage the antioxidant potential of natural foods to promote health and longevity.

7.1. Use of C. elegans in antioxidant and oxidative stress research

The nematode *Caenorhabditis elegans* (*C. elegans*) has emerged as a prominent model organism for studying oxidative stress and antioxidant mechanisms, largely due to its genetic similarities to humans, short lifespan, and well-characterized biology. This review aims to synthesize existing knowledge regarding *C. elegans* as a model for investigating antioxidant properties, elucidating mechanisms through which various compounds exert protective effects against oxidative stress.

The utilization of *C. elegans* in antioxidant research is well-supported by its well-mapped genome and the availability of numerous mutant strains, facilitating targeted studies on specific pathways related to oxidative stress resistance and aging. Significant advancements have been made in understanding the role of specific molecular pathways, particularly those involving transcription factors like DAF-16/FOXO. DAF-16 has been shown to mediate the oxidative stress response, with studies indicating that modulation of this pathway through dietary compounds can enhance the organism's stress resistance and longevity (Shi et al., 2012; Chen et al., 2021; Ayuda-Durán et al., 2020). Moreover, the connection between the antioxidant potential of phytochemicals and lifespan extension via the insulin/IGF-1 signaling pathway has been emphasized (Zhao et al., 2017; Chen et al., 2021; Ayuda-Durán et al., 2020).

Numerous studies demonstrate that various natural products exhibit antioxidant capacities when tested in *C. elegans*. For example, flavonoids and polyphenols have shown protective effects, primarily through their antioxidative activities (Shi et al., 2012; (Ayuda-Durán et al., 2020). In particular, the antioxidant effects of quercetin were enhanced when combined with sugar moieties, suggesting that the biomass composition of such compounds plays a crucial role in their bioavailability and efficacy (Cheng et al., 2014). Similarly, studies of polysaccharides from sources like *Auricularia auricular* and *Brassica chinensis* have highlighted their potential to mitigate oxidative stress and promote healthier aging in this nematode model (Fang et al., 2019; Chen et al., 2016b).

Moreover, the enzymatic activity related to the detoxification of reactive oxygen species (ROS) has also been studied extensively, revealing that antioxidant enzymes such as SOD and CAT play significant roles in the survival of *C. elegans* under oxidative stress conditions. Studies noted the induction of these enzymes in response to various stressors, suggesting that the organism's innate defense mechanisms are robust and can be influenced by dietary antioxidants or environmental conditions (Song et al., 2014; Li et al., 2013). The interaction between these enzymes and genetic modulators underscores the complexity of oxidative stress response networks that can potentially be targeted for therapeutic interventions against aging and associated oxidative damage Zhu et al., 2022; Li et al., 2013). Figure 3. Overview of *Caenorhabditis elegans* as an antioxidant model presented in this review. The figure highlights how *C. elegans* has been utilized to investigate antioxidant activity, oxidative stress pathways, and physiological responses relevant to antioxidant research.

8. Genetic insights into antioxidant activity

Research demonstrates that *C. elegans* offers valuable insights into how antioxidant compounds modulate cellular stress mechanisms. The nematode has been widely employed to assess the antioxidant potential of diverse natural products, including polyphenols and polysaccharides (Ayuda-Durán et al., 2020; Pang et al., 2024; Zhu et al., 2022). For example, polysaccharides isolated from *Dendrobium officinale* exhibited significant antioxidant activity when tested in *C. elegans*, highlighting the organism's utility in evaluating plant-derived antioxidants and their effects on oxidative stress (Pang et al., 2024). Similarly, compounds such as quercetin have demonstrated multiple biological activities, including neuroprotective effects, indicating that natural antioxidants can function via several pathways, many of which have been validated using *C. elegans* models (Schiavi et al., 2023).

The antioxidant pathways activated in *C. elegans*, such as the SKN-1/Nrf signaling pathway, are particularly important for mediating oxidative stress responses. Understanding these pathways is essential for elucidating mechanisms related to longevity, stress resistance, and metabolic health (Blackwell et al., 2015). One advantage of *C. elegans* lies in its genetic tractability; techniques like RNA sequencing (RNA-seq) have enabled the identification of key genes and regulatory networks involved in antioxidant defense, providing a molecular framework for studying these protective processes (Shen, 2025).

Natural antioxidants have also been shown to enhance the organism's resistance to oxidative stress. For instance, treatments with various selenium species have been reported to boost antioxidative defenses in *C. elegans*, with early supplementation producing long-lasting improvements in stress response capabilities (Rohn et al., 2019). Such findings suggest that dietary antioxidants can exert persistent beneficial effects on healthspan and resilience to oxidative damage.

Furthermore, the availability of transgenic *C. elegans* lines expressing fluorescent markers allows for dynamic visualization of antioxidant effects on cellular and physiological states. These tools enable real-time monitoring of how natural compounds influence oxidative stress and cellular function, deepening the mechanistic understanding of antioxidant action in vivo (Li et al., 2023b).

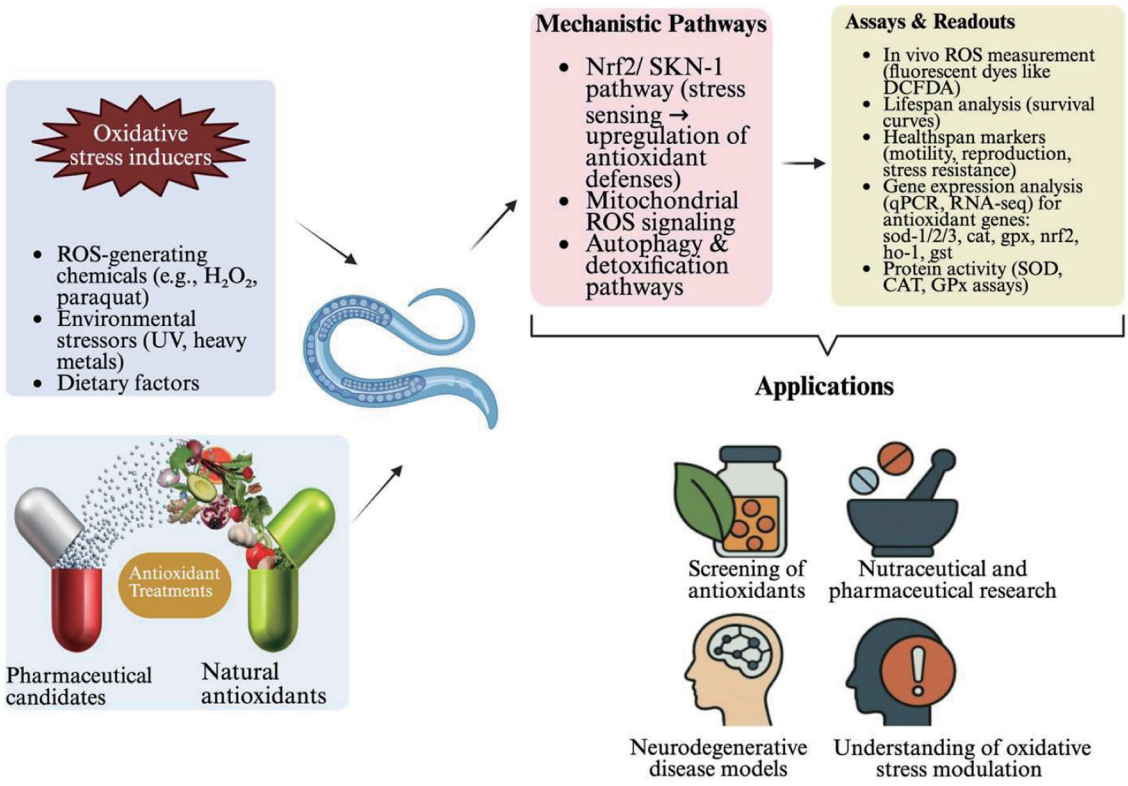

Figure 3. Overview of *Caenorhabditis elegans* as an antioxidant research model

9. Integrative omics of antioxidant mechanisms

Integrative omics studies utilizing *Caenorhabditis elegans* (*C. elegans*) as an experimental model have become a crucial approach for evaluating the antioxidant potential of various natural sources. By employing multi-omics strategies, including genomics, transcriptomics, proteomics, and metabolomics, researchers can gain a comprehensive understanding of antioxidant mechanisms, particularly in the context of oxidative stress and aging.

C. elegans is an effective in vivo model for antioxidant research due to its well-characterized genetics and conserved metabolic pathways. Critical signaling pathways associated with oxidative stress responses, such as the insulin/IGF-1 signaling pathway involving DAF-2/IGF-1R, AGE-1/PI3K, and DAF-16/FOXO, have been well established. Manipulation of these pathways has been shown to enhance lifespan and stress resistance, reflecting the organism's antioxidant capacity (Pang et al., 2023; Wang et al., 2022). Moreover, natural compounds have been reported to modulate these pathways, contributing to improved oxidative resistance and longevity in *C. elegans* (Zeng et al., 2021).

In integrative omics studies, the antioxidant effects of natural extracts have been assessed through metabolomic analyses. For instance, polysaccharides derived from mushrooms such as *Auricularia auricular* and *Lactarius deliciosus* demonstrated significant antioxidant activities, improving survival rates of *C. elegans* exposed to oxidative stress (Fang et al., 2019; Wang et al., 2022). Such studies commonly evaluate parameters including malondialdehyde levels, reactive oxygen species (ROS) accumulation, and the activity of antioxidant enzymes such as catalase and superoxide dismutase to determine the efficacy of natural compounds (Fang et al., 2019). Additionally, *C. elegans* serves as a reliable model for investigating the bioavailability and mechanistic action of these antioxidants (Lin et al., 2018).

The application of advanced omics technologies further clarifies the molecular pathways underlying antioxidant activity. Comprehensive multi-omics profiling has revealed metabolic remodeling in response to oxidative stress, including the upregulation of key antioxidant genes and stress-response markers (Wu et al., 2023). This integrative approach not only identifies potential antioxidants but also elucidates their biological effects, such as modulation of metabolic pathways and activation of stress response mechanisms (Wu et al., 2023).

Furthermore, studies using *C. elegans* have demonstrated the beneficial effects of dietary compounds, such as trigonelline, in enhancing oxidative stress resistance and promoting longevity (Zeng et al., 2021). These findings underscore the significance of diet-derived antioxidants in supporting healthspan, and integrative omics approaches provide a powerful framework for linking metabolic shifts to longevity and stress resilience in this model organism.

10. Dietary interventions for stress resistance

The exploration of dietary interventions to assess the antioxidant potential of natural sources using *Caenorhabditis elegans* (*C. elegans*) has gained considerable attention in pharmacological and nutraceutical research. *C. elegans* is valued as a model organism due to its genetic tractability, well-characterized biology, and the relevance of its oxidative stress response to human health.

A key aspect of using *C. elegans* for evaluating antioxidant activity is the modulation of crucial antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), which are essen-

tial in mitigating oxidative stress. For example, Liu et al. (2016) demonstrated that stereoisomeric forms of astaxanthin enhance the expression of these enzymes, thereby improving *C. elegans* resistance to oxidative stress induced by paraquat. Similarly, flavonoid compounds such as rutin from *Myrciaria tenella* have been shown to reduce reactive oxygen species (ROS) levels significantly, with Ribeiro et al. (2019) reporting notable reductions in ROS following rutin treatment. These studies highlight the critical influence of dietary compound structure and function on antioxidant efficacy.

Plant extracts have also been shown to modulate oxidative stress responses in *C. elegans*. Chen et al. (2016a) reported that *Centella asiatica* extract activates antioxidative defenses and may influence amyloid beta accumulation, suggesting potential neuroprotective effects, although further research is required. In addition, Arantes et al. (2018) observed that guarana extract downregulates stress-response genes, likely due to its inherent antioxidant properties, indicating a direct impact on cellular repair mechanisms. Collectively, these findings demonstrate how dietary interventions can influence aging processes and enhance the antioxidative capacity of *C. elegans*.

Various plant-derived compounds have also been associated with longevity and resilience against oxidative damage in *C. elegans*. Zhao et al. (2017) characterized emodin as a compound capable of stimulating insulin/IGF-1 signaling pathways, leading to increased lifespan and activation of antioxidant enzymes. Similarly, Zou et al. (2024) demonstrated that extracts from *Hemerocallis citrina* promote lifespan extension by regulating antioxidant enzymes and related genes. These results align with broader literature suggesting that dietary antioxidants can modulate signaling pathways, contributing to age-related health benefits.

11. Challenges and limitations

Our comparative analysis (Table 1) underscores that the three cornerstone model organisms—zebrafish, fruit fly, and *C. elegans*—each occupy a distinct niche in the research pipeline. Zebrafish, as vertebrates, are exceptionally valuable for direct translational applications in toxicology and disease modeling, leveraging their genetic homology and suitability for live imaging. Conversely, *D. melanogaster* and *C. elegans* serve as powerful discovery engines for initial screening and mechanistic inquiry; the fly excels in genetic dissection of pathways, while the worm is the premier model for high-throughput lifespan and stress resistance studies. This tiered approach, from simple invertebrates to more complex vertebrates, allows for efficient triaging of compounds and hypotheses before committing to higher-cost mammalian models.

The zebrafish (*Danio rerio*) model has gained prominence in antioxidant research due to its suitability for *in vivo* experimentation. Its advantages include rapid development, genetic similarities to humans, and the visibility of phenotypic changes through its transparent embryos (Wang et al., 2023a; Kim et al., 2021). However, several limitations exist when using zebrafish for antioxidant studies.

One primary concern is the potential variability in physiological responses among zebrafish. This variability can arise from factors such as genetic background, environmental conditions, and developmental stages. Variations in methodologies—such as exposure times and concentrations of tested compounds—may lead to inconsistent results in antioxidant assays (Arteaga et al., 2024). Different protocols can yield vastly different outcomes, amplifying the need for standardized procedures in zebrafish studies. This lack of standardization complicates the comparison of findings across different research groups and can hinder the reproducibility of antioxidant effects.

Another significant limitation is the disconnect between *in vitro* and *in vivo* responses. For instance, hydrogen peroxide (H_2O_2) failed to induce the Nrf2 pathway in tested zebrafish cell lines, which contrasts with responses observed in mammalian cells and in whole zebrafish embryos. This demonstrates that even optimized *in vitro* systems require validation in the whole organism to ensure physiological relevance (Lungu-Mitea et al., 2018). Moreover, a high antioxidant potential does not always guarantee a safe toxicological profile. Studies on Australian fruit extracts revealed that despite strong antioxidant activity, *in vivo* assessments still demonstrated potential toxic effects, underscoring the importance of comprehensive toxicological screening before pharmacological or nutraceutical application (Ali et al., 2022).

Additionally, the robustness of the zebrafish model in simulating human metabolic processes must be carefully evaluated. While zebrafish share many genetic and physiological similarities with humans, their responses to oxidative stress and antioxidant interventions are not always analogous. Some studies indicate that zebrafish exhibit a higher resistance to harmful agents compared to mammalian systems, which may lead to an underestimation of cytotoxic effects (Jaja-Chimedza et al., 2012; Wang et al., 2020). Zebrafish are also ectothermic, relying on glycolysis under fluctuating oxygen conditions and possessing a higher proportion of unsaturated fatty acids in their membranes, which makes them more prone to oxidative damage—traits that may not directly translate to human physiology (Fang and Miller, 2012).

Environmental variables can further confound experimental results. Water parameters, such as temperature and pH, significantly influence oxidative stress responses and metabolic rates, potentially skewing antioxidant assessments (Kim et al., 2021; Arteaga et al., 2024). Maintaining controlled laboratory conditions is crucial but challenging, particularly in large-scale experiments. Developmental stage differences also influence outcomes, as antioxidant responses observed in embryos may not reflect those in adult zebrafish due to differing metabolic states (Nguyen et al., 2018).

Finally, while the transparency of zebrafish embryos allows real-time imaging of oxidative stress markers, visual assessment methods yield largely qualitative data, which may not always correlate with quantitative biochemical measures. This raises the risk of overinterpreting antioxidant efficacy and highlights the need for complementary quantitative assays (Wang et al., 2023a; Arteaga et al., 2024).

Similar challenges exist in ecotoxicological research, where predicting the risk of chronic, low-level contaminant exposure is complex. Compounds such as arsenic trioxide and maduramicin can induce significant oxidative stress and cellular damage even at concentrations considered safe by regulatory standards, underscoring the need for improved risk assessment models in aquatic systems (Sarkar et al., 2014; Ni et al., 2019).

The fruit fly (*Drosophila melanogaster*) is also widely used in oxidative stress and antioxidant studies due to its genetic tractability and short lifespan. However, its simpler biological systems can limit translational relevance. For example, studies investigating antioxidants such as curcumin or vitamin C in *Drosophila* models of neurodegenerative diseases mimic human conditions only partially, with significant differences in pathophysiology (Nghi et al., 2022; Anh et al., 2019). This raises concerns about the direct applicability of findings to humans, as certain cellular pathways and regulatory mechanisms may differ substantially (Hwang et al., 2013; Mockett et al., 1999).

Genetic manipulation is common in *Drosophila* research but can introduce unintended phenotypes that confound results. Over-

expression of antioxidant enzymes such as glutathione reductase altered longevity and stress resistance under hyperoxic conditions but did not fully represent mild oxidative stress responses (Mockett et al., 1999; Aigaki et al., 2004). Similarly, transgenic models of human disease may not capture the full genetic and environmental variability of human populations (Jahromi et al., 2013).

Methodological issues also arise from the use of chemical assays such as DPPH radical scavenging tests, which may not capture the complexity of oxidative stress in living organisms (Ndinawe and Kinyi, 2021; Yang et al., 2021). Antioxidants showing strong *in vitro* activity may display very different efficacy in vivo due to metabolism and bioavailability differences (Dias-Santagata et al., 2007; Zhong et al., 2022). Furthermore, acute oxidative stress models (e.g., paraquat exposure) may not reflect the chronic oxidative stress that underlies most human diseases, risking a bias toward short-term protective mechanisms (Seong et al., 2015).

The nematode *Caenorhabditis elegans* (*C. elegans*) is another valuable model for oxidative stress research due to its genetic tractability and conserved stress response pathways. However, strain-specific responses to oxidative stress inducers such as H_2O_2, paraquat, and sodium arsenite can complicate interpretation (Lee et al., 2006; Chen et al., 2024). Moreover, antioxidants may exert dual effects, enhancing resistance at certain doses but inducing stress at others (Kim and Park, 2020; Liu et al., 2021a; Wu et al., 2022; Chen et al., 2022). Genetic modifications—such as transgenic overexpression of stress-related genes—can further skew results and limit extrapolation to wild-type organisms (Ma et al., 2016; Benedetto et al., 2010).

Beyond these methodological challenges, *C. elegans* studies face general limitations regarding translatability to human biology. Despite sharing conserved signaling pathways such as DAF-2/IGF-1R and DAF-16/FOXO, species-specific differences in pathway regulation can impact the interpretation of results (Pang et al., 2023; Zou et al., 2024). The nematode's short lifespan (2–3 weeks) restricts long-term aging studies, and its laboratory environment fails to replicate key factors such as gut microbiota interactions, which are critical for antioxidant metabolism in humans (Reigada et al., 2022; Barreto et al., 2020). Furthermore, dose-response relationships often fail to correspond to physiologically relevant human intakes (Pang et al., 2023; Wang et al., 2022).

Finally, *C. elegans* lacks behavioral and physiological complexity, limiting its usefulness in studying the neurological and systemic impacts of oxidative stress (Zou et al., 2024; Arantes et al., 2018). Therefore, while *C. elegans* provides mechanistic insights into oxidative stress and aging, validation in more complex mammalian models remains essential for translating findings to human health (Morcos and Hutter, 2009; Zhang et al., 2021).

12. Applications and future direction

Scientists often use simple animals to study how antioxidants work. These animals are useful because they are easy to grow and their genes are easy to study. Table 1 shows how three common animals—the zebrafish, fruit fly, and a tiny worm called *C. elegans*—are used to find and test new antioxidants. A significant direction in antioxidant research involves the development of sophisticated in vitro assays using zebrafish cell lines. The establishment of Nrf2-responsive reporter gene assays in lines such as ZFL and ZF4 offers an effective alternative to *in vivo* testing. This aligns with the 3Rs principle (Replacement, Reduction, and Refinement), enabling high-throughput screening of chemicals and environmental samples for oxidative stress potential, thereby accelerating toxicological risk assessment (Lungu-Mitea et al., 2018). In parallel, the screening of natural antioxidants from sources like marine algae is gaining momentum. For instance, sulfated polysaccharides from *Sargassum tenerrimum* have shown efficacy in mitigating oxidative damage in both cellular and whole-organism models, pointing to novel nutraceutical and pharmaceutical candidates (Raguraman et al., 2019). Zebrafish are also increasingly used to evaluate the therapeutic potential of novel compounds for complex diseases. Studies on metabolites such as cotinine and 6-hydroxy-L-nicotine demonstrate their utility in assessing multi-target agents that improve cholinergic function, reduce oxidative stress, and enhance neuroprotective gene expression, making them promising leads for cognitive disorders like Alzheimer's disease (Szychlinska and Marino Gammazza, 2025).Furthermore, the integration of CRISPR/Cas9-based genetic manipulation enables precise investigation of disease mechanisms and treatment responses, advancing personalized medicine approaches with zebrafish models (Hong and Luo, 2021) (Table 2).

Similarly, *Drosophila melanogaster* provides unique opportunities for advancing antioxidant research beyond traditional lifespan and stress-resistance assays. Emerging studies advocate incorporating multi-omics strategies—transcriptomics, proteomics, and metabolomics—to map molecular networks modulated by dietary antioxidants. These approaches can identify target genes, signaling pathways, and molecular interactions underlying antioxidant effects while also clarifying the long-term impact of sustained phytochemical exposure on oxidative stress–related diseases. Comparative analyses across diverse *Drosophila* strains or closely related species may further reveal how genetic variability contributes to antioxidant responses, enriching our understanding of gene–diet interactions. Such efforts will not only highlight protective effects but also uncover potential adverse impacts of prolonged antioxidant intake, thereby enhancing the translational value of *Drosophila* in functional food and nutraceutical research.

The nematode *Caenorhabditis elegans* (C. elegans) also remains central to oxidative stress research, particularly in aging and antioxidant defense studies. Future directions include probing gene regulation mechanisms, where transcription factors like DAF-16 (FoxO orthologue) and NHR-49 mediate stress tolerance and longevity by activating detoxification genes such as *gst-4* and *gcs-1* (Hu et al., 2018; Chen et al., 2024; Liu et al., 2021b). Natural antioxidants such as rosmarinic acid and phenolic compounds modulate insulin signaling pathways, enhance antioxidant defenses, and extend healthspan (Lin et al., 2019; Saier et al., 2018). Polyphenols and carotenoids further exhibit dual functions in scavenging ROS and enhancing endogenous defenses, though their effects depend on dose and gut microbiota interactions (Llopis et al., 2019; Zhang et al., 2019; González-Peña et al., 2021; Ayuda-Durán et al., 2022). Beyond longevity, oxidative stress intersects with neurodegenerative models, where early oxidative damage has been shown to precede β-amyloid accumulation in Alzheimer's disease models (Moliner et al., 2019; Chin et al., 2024). Advanced technologies such as microfluidics now facilitate high-throughput drug screening, accelerating the discovery of compounds targeting oxidative stress pathways (Wang et al., 2019). Collectively, these advances highlight the expanding role of *C. elegans* in deciphering oxidative stress biology and identifying therapeutic interventions.

13. Conclusion

Small animal models such as zebrafish (*Danio rerio*), *Caenorhabditis elegans*, and fruit fly (*Drosophila melanogaster*) remain in-

Table 2. Use of Zebrafish, Fruit Fly, and *C. elegans* for Antioxidant Discovery

Compound/Extract	Source	Key Findings in Zebrafish	Mechanisms/Pathways	References
Zebra fish model				
Water Extract of Citrus Pomace	Citrus Pomace	Improved survival rates; reduced heartbeat and ROS levels.	Scavenging of free radicals; reduction of cell death.	Wang et al., 2018
Heat-killed LAB Strains	Various Lactic Acid Bacteria	Reduced H_2O_2-induced toxicity; all strains showed antioxidant activity.	Indirect antioxidant activity; activation of antioxidant enzymes.	Sato et al., 2024
Rutin Trihydrate	Not specified	Increased GPx (9%), GSH (5%), GST (5%); countered doxorubicin effects.	Upregulation of key antioxidant enzymes; oxidative stress response.	Seethalakshmi and Kumar, 2024
6-Gingerol	Ginger	Reduced ROS and cell death; ↑SOD and CAT; ↓lipid peroxidation in larvae.	Direct antioxidant activity; regulation of ROS and H_2O_2.	Manjunathan et al., 2021
Naringenin	Citrus, food sources	Protective against oxidative stress-induced lethality.	Induction of antioxidant pathways (e.g., Nrf2).	Arteaga et al., 2021
Apigenin	Parsley, food sources	Protective against lethality and dysmorphogenesis.	Activation of cellular protective responses.	Arteaga et al., 2021
Rutin	Buckwheat, food sources	Protective against lethality and dysmorphogenesis.	Enhanced oxidative stress resistance.	Arteaga et al., 2021
Oleuropein	Olive, food sources	Protective against oxidative stress-induced lethality.	Modulation of oxidative stress mechanisms.	Arteaga et al., 2021
Chlorogenic Acid	Coffee, food sources	Protective against oxidative stress-induced lethality.	Support of antioxidant defense systems.	Arteaga et al., 2021
Curcumin	Turmeric, food sources	Protective against lethality and dysmorphogenesis.	Activation of Nrf2 and other protective pathways.	Arteaga et al., 2021
Lycopene	Tomato, food sources	Protective against oxidative stress-induced lethality.	Enhancement of antioxidant pathways.	Arteaga et al., 2021
Astaxanthin	Algae, food sources	Protective against oxidative stress-induced lethality.	Modulation of cellular oxidative stress response.	Arteaga et al., 2021
β-Carotene	Carrot, food sources	Increased lethality and dysmorphogenesis at tested conditions.	Potential pro-oxidant effects at certain concentrations.	Arteaga et al., 2021
Carnosine	–	Decreased ROS in larvae; rescued Hsp70 and MT expression altered by TiO_2 NPs.	Antioxidant activity counteracting TiO_2 nanoparticle-induced oxidative stress.	Caruso et al., 2023
Phosvitin	Zebrafish Egg Yolk	Effective antioxidant; inhibited linoleic acid oxidation; non-cytotoxic.	Scavenges DPPH radicals; protects biomolecules from oxidation.	Hu et al., 2015
Chlorogenic Acid	Sonchus oleraceus (Sowthistle)	Reduced phenotypic abnormalities in embryos exposed to pro-oxidant auranofin.	Protective effects against oxidative stress and malformation.	Chiu et al., 2020
Nrf2 Inducers	Various Compounds	Induced expression of antioxidant genes (HO-1, NQO1, GSTs).	Activation of the Nrf2-ARE pathway.	Jung and Kwak, 2010
Quercetin Nanocrystals	Nanosuspension	Enhanced survival rates (66.67–77.78%) in H_2O_2-treated zebrafish.	Reduced ROS levels; catalyzed increased CAT and GPx activity.	Wang et al., 2023a
Glutathione (GSH)	Endogenous System	Robust antioxidant system; oxidized by ROS forming GSSG.	Involves GPx and GR; key oxidative stress marker.	Massarsky et al., 2017
N/A (Review on Drug Screening)	N/A	Review of zebrafish as a model for novel anti-inflammatory drug screening.	Analysis of inflammatory response and leukocyte behavior.	Xie et al., 2021

(continued)

Table 2. *(continued)*

Compound/Extract	Source	Key Findings in Zebrafish	Mechanisms/Pathways	References
Lignin-Carbohydrate Complexes	Wheat Stalk	Protected against BPA-induced neurotoxicity; reduced ROS and neuronal damage.	Suppressed nerve-related gene expression; reduced oxidative stress.	Gu et al., 2021
Polyphenolic Extract	Condalia microphylla Fruits	Inhibited lipid oxidation by up to 40% under oxidative stress.	Antioxidant activity; reduction of oxidative stress.	Boeri et al., 2017
Catechol	Experimental Compound	Increased ROS, reduced antioxidant capacity; decreased locomotor activity, increased anxiety.	Induction of redox imbalance; behavioral disruption.	Xiao et al., 2025
Equol	Soy	Exerts strong antioxidant effects.	Functions through an Nrf2-independent mechanism.	Watanabe et al., 2022
Total Particulate Matter (TPM)	Cigarette Smoke	Increased mortality, delayed hatching, deformities, and behavioral changes.	Disrupted angiogenesis; affected xenobiotic metabolism and oxidative stress.	Massarsky et al., 2015
tBOOH	Oxidant (Positive Control)	Induces oxidative stress in zebrafish embryos.	Used as a model oxidant to test protective effects of antioxidants.	Boix et al., 2020
TCHQ	Oxidant (Positive Control)	Induces oxidative stress in zebrafish embryos.	Used as a model oxidant to test protective effects of antioxidants.	Boix et al., 2020
LPS	Escherichia coli	Induces oxidative stress in zebrafish embryos.	Used to model inflammatory/oxidative stress to test antioxidants.	Boix et al., 2020
Momordica cochinchinensis Extract	Gac Fruit	Improved locomotor functions in an MPTP-induced Parkinson's disease model.	Not linked to significant change in antioxidant enzyme activities.	Singsai et al., 2023
Formulated Agar 1	Turbinaria conoides (Seaweed)	Higher antioxidant activity; lower teratogenic effects.	Demonstrates dose-dependent antioxidant potential.	Aavula et al., 2022
Formulated Agar 2	Turbinaria conoides (Seaweed)	Lower antioxidant activity; higher teratogenic effects.	Demonstrates dose-dependent toxicity.	Aavula et al., 2022
Curcumin	Turmeric	Reduces hydrogen peroxide-induced toxicity.	Nrf2-dependent pathway activation.	Endo et al., 2020
Diallyl Trisulfide	Garlic	Reduces hydrogen peroxide-induced toxicity.	Nrf2-dependent pathway activation.	Endo et al., 2020
Quercetin	Various plants	Reduces hydrogen peroxide-induced toxicity.	Nrf2-dependent pathway activation.	Endo et al., 2020
Cinnamaldehyde	Cinnamon	Reduces arsenite toxicity; exhibits antioxidant effects.	Nrf2-independent pathway.	Endo et al., 2020
Carnosic Acid	Rosemary	Toxic at high concentrations; antioxidant analysis inconclusive.	Proposed Nrf2 pathway; confounded by toxicity.	Endo et al., 2020
Troxerutin	Semi-synthetic flavonoid	Reduced MPO, NO, and LPO; protective against nicotine-induced lung fibrosis.	Scavenges free radicals; enhances defense; suppresses IL-10 & IL-1β expression.	Hobani, 2023
Dieckol	Ecklonia cava (Brown seaweed)	Reduced ROS, nitric oxide, and cell death induced by UVB radiation.	Direct antioxidant activity; protective against UVB-induced damage.	Ko et al., 2010
Antioxidant Peptides	C-phycocyanin (from algae)	Protective against H_2O_2-induced oxidative stress.	Activation of Nrf2 signaling pathway.	Xu et al., 2022
Lignin–carbohydrate complexes (LCCs)	Bamboo and Poplar	Scavenged endogenous ROS effectively.	Prevented reduction of antioxidant enzyme activity (SOD, CAT).	Dong et al., 2019

(continued)

Table 2. *(continued)*

Compound/Extract	Source	Key Findings in Zebrafish	Mechanisms/Pathways	References
Fruit fly model				
Cyanidin-3-O-glucoside (Anthocyanin)	Lonicera pallasii (Honeysuckle)	Increased lifespan and stress resistance; improved intestinal barrier integrity	Sirt6 activation; regulation of Hif1 & Keap1	Golubev et al., 2022
Mangifera indica leaf extract	Mangifera indica (Mango)	Enhanced survival; ↑GST, CAT activity; ↑thiol content	Enzyme induction (dose-sensitive)	Alexander et al., 2019
Astragalus membranaceus extract (AME)	Astragalus membranaceus	Enhanced survival under H_2O_2 challenge; ↓ROS; ↑SOD, CAT; ↑Sod1, Cat, CncC	Enzyme induction; gene regulation	Dai et al., 2024
Curcumin	Turmeric	Lifespan extension (males); reversed by SOD inhibitor	SOD-dependent pathway	Suckow and Suckow, 2006
Flavonoids (icariin, epimedins A–C)	Epimedium pubescens	Enhanced radical-scavenging; boosted CAT, GSH-Px	Antioxidant enzyme activation	Yang et al., 2020
Proanthocyanidin-rich fraction	Tamarindus indica	Improved lifespan, emergence rate, antioxidant enzyme activity; ↓AChE, caspase-3/9	Antioxidant enzyme activation; neuroprotection	Jaafaru et al., 2024
Artemisia argyi extract	Artemisia argyi	Prolonged lifespan; improved climbing; ↑stress tolerance; enzyme modulation; ↓MDA	SOD, CAT modulation	Yang et al., 2024
Phlorizin	Apple	Lifespan extension; improved locomotion; ↑Nrf2/cnc, ↓methuselah	Nrf2 activator; stress regulation	Wang et al., 2019
Crimson snapper scale peptides	Marine fish	Extended lifespan; ↓MDA, protein carbonylation; ↑SOD, CAT	Upregulation of SOD1, SOD2, CAT	Chen et al., 2020
Rice protein hydrolysates	Rice	Increased lifespan; boosted SOD, Mn-SOD, CAT	Nrf2/Keap1, TOR/S6K, methuselah modulation	Yue et al., 2021
Casein peptides	Milk protein	Improved survival; restored GSH, thiols, proteins; normalized oxidative markers	Keap1/Nrf2 regulation	Sadiq et al., 2023
Lateolabrax japonicus peptides (LPH)	Japanese seabass	Extended lifespan; ↓ROS, MDA; ↑SOD, CAT, GSH-Px; preserved gut integrity	Nrf2 activation; mTOR downregulation; gut microbiota modulation	Li et al., 2023b
C. elegans model				
Rhein Derivative 4b	Rhein	Increases lifespan & stress resistance; enhances GSH; reduces MDA & ROS	Targets Keap1-Nrf2 pathway	Wang, 2025
Monascus-fermented Dioscorea (RMDE)	Yam	Increases survival during oxidative stress; reduces ROS	DAF-16/FOXO-dependent pathway; induces *sod-3* expression	Shi et al., 2012
Magnolol Derivative M27	Houpoea officinalis	Prolongs lifespan; improves healthspan; increases stress resistance	IIS pathway (DAF-2, AGE-1, DAF-16)	Pang et al., 2023
Polyphenols	Blumea laciniata	Extends lifespan (17.4%); enhances stress resistance; reduces ROS & MDA	Insulin/IGF-1 signaling; promotes DAF-16 nuclear translocation	Chen et al., 2021
Caffeic Acid Phenethyl-ester (CAPE)	Propolis	Increases stress resistance & lifespan (9–17%); reduces ROS	Modulates DAF-16 signaling pathway; SKN-1 independent	Havermann et al., 2014

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Table 2. *(continued)*

Compound/Extract	Source	Key Findings in Zebrafish	Mechanisms/Pathways	References
Methanol Extract	Camellia tenuifolia	Prolongs lifespan; reduces amyloid-β toxicity	Decreases intracellular ROS levels	Wei et al., 2014
Kaempferol Glycosides	Camellia tenuifolia	Decreases ROS levels; prolongs lifespan	Antioxidant and anti-inflammatory activities	Wei et al., 2014
Hot Water Extract	Chamaecyparis obtusa	Extends lifespan; decreases lipofuscin	Enhanced antioxidant activity via flavonoid absorption	Cheng et al., 2014
Guarana	Paullinia cupana	Extends lifespan; antioxidant activity	DAF-16, HSF-1, SKN-1 pathways	Arantes et al. 2018
Selenite	–	Protects from oxidative stress	DAF-16 and TRXR-1 dependent	Li et al., 2013
Oleuropein	Olive	Prolongs lifespan (22.3%); increases survival against stress	Insulin/IGF-1 and SKN-1/Nrf2 signaling pathways	Fang and Miller, 2012
Yeast Hydrolysate	Yeast	Enhances lifespan and stress resistance	Modulates tyrosine, glycerophospholipid, and glutathione metabolism	Li et al., 2023a
Guarana	Paullinia cupana	Lifespan extension; high antioxidant capacity	Indirect effects via altering *E. coli* metabolism	Reigada et al., 2022
Phenolic Compounds	*Sonchus arvensis*, *Hemerocallis citrina*	Improves lifespan & health against nutrient stress	TGF-β signaling pathway; *skn-1*	An et al., 2023
Cassia fistula Extract	Cassia fistula	Improves survival; reduces ROS & proteotoxicity	DAF-16/FOXO and SKN-1/NRF2 pathways	Thabit et al., 2018
Carbendazim	Fungicide	Inhibits growth & lifespan; damages reproduction & antioxidant systems	Impairs oxidative stress response; toxic	Li et al., 2020
Liuwei Dihuang (LWDH)	Traditional Chinese Medicine	Delays β-amyloid paralysis; reduces ROS	Upregulation of HSPs; antioxidant activity	Sangha et al., 2012
Ethyl Acetate Extract	Gastrodia elata	Protects from oxidative stress & Aβ toxicity; improves lifespan	Insulin/IGF-1 signaling (IIS) pathway	Shi et al., 2023
Acrolein	Toxic Aldehyde	Shortens lifespan; increases ROS; decreases healthspan	Activates DAF-16/FOXO stress response	Jeayeng et al., 2024
Leaf Extract	*Anacardium occidentale* (Cashew)	Enhances stress survival & lifespan; reduces lipofuscin	DAF-16/FoxO & SKN-1/Nrf-2 pathways; induces *sod-3*, *gst-4*	Duangjan et al., 2019
Polysaccharides	*Dendrobium officinale*	Prolongs lifespan; increases antioxidant enzyme activity	Upregulation of *daf-16*, *skn-1*, *sir-2.1*	Tang et al., 2023
Total Flavonoids	Sea Buckthorn	Increases lifespan (29.4%); enhances stress tolerance; delays paralysis	Radical scavenging; AChE/MAO-A inhibition	Wang et al., 2022
Polysaccharides	Fermented Coix Seed	Increases lifespan (5.9%); enhances antioxidant enzymes	Downregulates *daf-2*, *age-1*; upregulates *daf-16*, *sod-3*, *skn-1*	Zhao et al., 2023
Cannabidiol (CBD)	*Cannabis sativa*	Extends lifespan & survival in AD model	Activates neural glyoxalase pathway; detoxifies methylglyoxal	Frandsen and Narayanasamy, 2022
Extract	*Anoectochilus roxburghii*	Prolongs lifespan; reduces ROS; increases stress resistance	Activation of *daf-16*/FoxO pathway	Xu et al., 2024

valuable in vivo systems for studying dietary antioxidants. Their short lifespans, rapid reproduction, ease of genetic manipulation, conserved molecular pathways, and genetic homology to humans make them ideal for mechanistic investigations and high-throughput screening. These models enable detailed evaluation of bioavailability, absorption, metabolism, and antioxidant mechanisms, while providing functional insights into resistance to oxidative stress, age-related disorders, metabolic and neurological health, and potential lifespan extension.

However, translation of these findings to human health requires careful consideration of interspecies differences, including metabolism, gut physiology, microbiota composition, and dose scaling. For instance, differences in intestinal absorption rates, enzymatic biotransformation, and systemic distribution of antioxidants may lead to variability in efficacy between model organisms and humans. Standardization of assay conditions, dietary delivery, and exposure protocols is essential to improve reproducibility and comparability across studies.

Importantly, data from these models can guide the design of human trials and functional food development by identifying candidate bioactive compounds, elucidating molecular targets, and predicting safety profiles before advancing to mammalian models or clinical research. Advances in CRISPR-based genome editing, live imaging, metabolomics, and multi-omics integration continue to enhance the translational relevance of these models, bridging the gap between discovery science and evidence-based nutritional interventions. Collectively, these organisms represent cost-effective, ethically viable platforms that not only accelerate antioxidant research but also inform precision nutrition strategies and the rational design of functional foods and nutraceuticals for mitigating oxidative stress–related diseases in humans.

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