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Anti-aging potential of plant-derived compounds in Drosophila melanogaster

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Abstract
The exploration of plant-derived compounds for anti-aging interventions has garnered significant attention, with *Drosophila melanogaster* serving as a pivotal model organism due to its genetic tractability and conserved aging pathways. Recent studies have highlighted the efficacy of various phytochemicals in modulating lifespan and enhancing stress resistance in *Drosophila.* Ginseng extract, rich in ginsenosides, has been shown to extend the lifespan of *Drosophila* by approximately 9.72%. This effect is attributed to the activation of the AMPK pathway and inhibition of the mTOR pathway, leading to improved energy metabolism and stress resilience. Similarly, caffeic acid, a phenolic compound, has demonstrated protective effects against age-associated intestinal dysplasia by suppressing oxidative stress-induced JNK signaling, thereby maintaining intestinal stem cell function. Flavonoids, a diverse group of polyphenolic compounds found in various plants, exhibit potent antioxidant and anti-inflammatory properties. Their role in mitigating oxidative damage and modulating signaling pathways associated with aging underscores their potential as anti-aging agents. The mechanisms underlying the anti-aging effects of these phytochemicals involve the modulation of key genetic pathways, including the upregulation of sirtuins (e.g., SIRT1), activation of AMPK, and suppression of mTOR signaling. These pathways collectively contribute to enhanced autophagy, improved mitochondrial function, and reduced cellular senescence.

Keywords: Plant-derived compounds, Drosophila melanogaster, Aging, Lifespan, Healthspan, Oxidative Stress, Inflammation, Mitochondrial Function, Insulin Signaling

1. Introduction

Aging is an intrinsic biological process marked by the progressive decline in physiological functions, ultimately increasing susceptibility to various diseases and leading to mortality [1]. The search for interventions capable of delaying aging and promoting a longer healthspan has gained significant traction in contemporary biomedical research. Among the emerging strategies, plant-derived compounds, collectively termed phytochemicals, have attracted attention due to their broad spectrum of bioactivities and generally low toxicity profiles. In this context, *Drosophila melanogaster*, commonly known as the fruit fly, has served as a powerful model organism for aging research. Owing to its short lifespan, well-mapped genome, and conserved aging-associated pathways, Drosophila provides a convenient and informative platform for investigating the mechanisms and efficacy of anti-aging agents. Importantly, many fundamental biological processes involved in aging—such as oxidative stress response, mitochondrial function, metabolic regulation, and gene expression—are evolutionarily

conserved between Drosophila and mammals, lending relevance to translational studies. Phytochemicals such as polyphenols, flavonoids, and alkaloids have demonstrated the capacity to influence aging in Drosophila by modulating stress resistance, enhancing mitochondrial activity, and regulating key signaling cascades, including the insulin/IGF-1 and TOR pathways. Notably, compounds such as resveratrol, curcumin, catechins, and quercetin have been shown to extend lifespan and improve physiological robustness in fruit flies, often through antioxidant mechanisms and transcriptional regulation. Given the growing body of evidence supporting the role of phytochemicals in mitigating age-related decline, this review focuses on the anti-aging potential of four well-characterized plant-derived compounds—resveratrol, curcumin, silibinin, and quercetin—in *Drosophila melanogaster* and relevant experimental models, highlighting their mechanisms of action, effects on lifespan and healthspan, and prospects for future research.

2. Review of literature

Aging is a multifactorial biological process associated with cellular degeneration, oxidative stress, and altered gene regulation. *Drosophila melanogaster* serves as a valuable model for aging studies due to its genetic similarity to humans, short lifespan, and well-characterized pathways (Piper & Partridge, 2018). Plant-derived compounds have emerged as promising anti-aging agents, mainly owing to their antioxidant, anti-inflammatory, and lifespan-extending properties. Resveratrol, a polyphenol found in grapes, has shown to extend lifespan in *Drosophila* through activation of the sirtuin (Sir2) pathway (Wood et al., 2004; Bauer et al., 2004). Similarly, curcumin, a curcuminoid derived from turmeric, has been reported to enhance lifespan and improve locomotor activity in aged flies via modulation of oxidative stress markers and enhancement of antioxidant enzyme activities (Lee et al., 2010; Chin et al., 2014). Another promising compound, quercetin, a flavonoid present in many fruits and vegetables, demonstrates antioxidant properties and modulates aging-related genes such as *foxo* and *SOD2*, leading to increased longevity in *Drosophila* (Peng et al., 2012; Castillo-Quan et al., 2016). Silibinin, extracted from milk thistle, has been found to attenuate neurodegeneration and oxidative damage in fly models of Parkinson's and Alzheimer's disease, indirectly contributing to improved lifespan and vitality (Bourre et al., 2013; Abd Elwahab et al., 2022). Moreover, compounds like epigallocatechin gallate (EGCG) from green tea (Zhang et al., 2009), catechins, and kaempferol have also been studied for their hormetic effects in *Drosophila*, often enhancing resistance to oxidative stress and extending lifespan (Peng et al., 2012; Bahadorani et al., 2008).Mechanistically, these phytochemicals exert anti-aging effects by targeting pathways such as insulin/IGF-1 signaling (IIS), mTOR, AMPK, and JNK, which are conserved from flies to humans (Fontana et al., 2010). Studies have also documented the ability of these compounds to regulate autophagy, proteostasis, and mitochondrial function, which are critical in delaying age-related decline (Pletcher et al., 2002; Zhang & Herman, 2020). Notably, combinations of phytochemicals or synergistic formulations have shown greater efficacy than individual compounds, suggesting multi-targeted approaches may be superior (Wang et al., 2013).

2.1 Resveratrol

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a polyphenolic stilbene found in grapes, berries, and peanuts—is one of the most extensively studied plant-derived compounds for lifespan and healthspan modulation. In multiple model organisms, it was first reported to extend lifespan via activation of the NAD^+ -dependent deacetylase Sir2 (dSir2 in flies), mimicking dietary restriction (DR) effects, including enhanced fecundity—a hallmark distinct from DR alone (Howitz et al., 2003; Wood et al., 2004). Yet, its efficacy in *Drosophila* remains inconsistent. Some studies have failed to replicate longevity gains or stress-resistance benefits in standard wild-type strains at moderate doses (e.g., 500 µM in *w^1118*) (Bass et al., 2007; Pacholec et al., 2010). This variability appears strongly influenced by sex and nutritional environment (Gruber et al., 2007; Wang et al., 2014). Notably, resveratrol at 200–400 µM extended lifespan in females on calorie-rich, high protein or high fat diets—but had no effect under standard or high sugar, low protein regimens (Wang et al., 2014). Lifespan extension correlated with downregulation of insulin-like peptides (*dIlp3*, *dIlp5*) and oxidative-stress genes (e.g., *gstD1*, *hsp68*, peroxiredoxins), hinting at reduced insulin/IGF-like signaling and JNK-mediated stress protection (Rogina & Helfand, 2004; Grönke et al., 2010). Though resveratrol's influence on sirtuins is debated—some evidence challenges direct activation (Pacholec et al., 2010)—it consistently interacts with AMPK, PGC-1α, and autophagy pathways, promoting mitochondrial biogenesis and stress resilience (Price et al., 2012; Lagouge et al., 2006). Notably, enriched resveratrol rice strains significantly increased lifespan across two wild-type *Drosophila* lines (e.g., ORR, Harwich), underscoring dose/matrix effects (Lee et al., 2018).

Beyond lifespan, resveratrol shows neuroprotective promise. In Parkinson's disease (PD) fly models (e.g., *parkin*, MPTP, *PINK1* mutants), dietary resveratrol improved survival, climbing behavior, and mitochondrial health, while modulating redox balance, autophagy, and inflammation via *dSarm* repression (Wu et al., 2018; Guo et al., 2020). These findings affirm its dual role as an antioxidant and senomorphic agent, though high doses may elicit pro-oxidant or even cytotoxic effects (Ristow, 2014; Hori et al., 2013).

2.2 Curcumin

The principal bioactive diarylheptanoid in turmeric (Curcuma longa) is well recognized for its antioxidant, anti-inflammatory, and neuroprotective properties (Aggarwal & Harikumar, 2009). *Drosophila melanogaster* has proven to be a valuable in vivo model for evaluating curcumin's anti-aging potential, owing to its short lifespan, genetic tractability, and conservation of key aging-related signaling pathways (Piper & Partridge, 2018). Dietary supplementation with curcumin has been shown to significantly extend lifespan in several *Drosophila* strains. A landmark study by Lee et al. (2010) reported that curcumin administered at 0.5–1.0 mg/g diet prolonged mean lifespan by 12–26%, with the effects being both strain- and sex-dependent: female flies responded more robustly to lower doses, whereas male flies exhibited greater lifespan gains at higher concentrations. This dose-response relationship was corroborated by Chin et al. (2014), who also found that co-administration of the superoxide dismutase (SOD) inhibitor disulfiram abolished the lifespan-extending effects of curcumin, underscoring the pivotal role of SOD-mediated antioxidant defense in its mechanism of action. Beyond longevity, curcumin has been found to enhance several physiological healthspan

markers in *Drosophila*, including improved locomotor performance, increased stress resistance, extended reproductive lifespan, and enhanced progeny viability (Sharma et al., 2021). For example, curcumin-treated flies exhibited elevated aconitase activity, indicating improved mitochondrial function that benefits both adult physiology and early developmental stages (Lee et al., 2010). In neurodegenerative models, particularly those mimicking Parkinson's disease (PD), curcumin significantly reduced oxidative stress and apoptosis in the brain, thereby delaying functional deterioration and improving lifespan and behavior (Phom et al., 2014; Siddique et al., 2014). Mechanistically, curcumin's pro-longevity effects are multifactorial. It enhances antioxidant defense by upregulating SOD activity, a critical enzyme for detoxifying reactive oxygen species (Chin et al., 2014). This antioxidative mechanism has been directly linked to its life-extending effects, as inhibition of SOD completely abolishes curcumin's efficacy (Lee et al., 2010).

Moreover, curcumin induces transcriptional remodeling of key aging-related genes such as *mth*, *thor*, *InR*, and JNK early in the aging process, suggesting that it reprograms gene expression to favor longevity (Sharma et al., 2021). Microarray-based pathway analyses have associated curcumin's action with regulatory networks involving Notch, Wnt, p53 signaling, ribosomal biogenesis, and cell cycle control—pathways essential for organismal homeostasis and stress adaptation (Phom et al., 2014). It also improves mitochondrial metabolism, as evidenced by increased aconitase activity and more efficient energy utilization (Lee et al., 2010). Curcumin contributes to stress resilience through enhanced tolerance to environmental insults such as heat and genotoxic stress, possibly through activation of antioxidant and DNA repair pathways (Siddique et al., 2014). Though not yet directly confirmed in flies, curcumin may also induce autophagy via mTOR/TORC1 inhibition, as suggested by mammalian studies (Pallauf et al., 2016). In addition, it exhibits neuroprotective and anti-apoptotic effects by mitigating lipid peroxidation, protein oxidation, α-synuclein aggregation, and neuronal cell death in PD fly models, all of which contribute to improved neurobehavioral outcomes (Phom et al., 2014). Curcumin's effectiveness in *Drosophila* is modulated by dose, sex, genetic background, and environmental stress levels. Females appear to benefit from lower doses under baseline conditions, while males and flies under stress require higher concentrations (Lee et al., 2010; Chin et al., 2014). However, excessive supplementation (e.g., with crude turmeric powder) may impair locomotion or fertility, indicating a hormetic response curve (Pallauf et al., 2016). This underscores the necessity for careful dose optimization. Curcumin's broad spectrum of action—encompassing oxidative stress mitigation, gene network modulation, mitochondrial support, and neuroprotection—makes it a strong candidate for aging interventions. Nevertheless, its application in mammalian systems is limited by poor bioavailability and chemical instability (Anand et al., 2007). To overcome these challenges, future *Drosophila* research should focus on mapping precise dose-response relationships across different genetic and physiological contexts, investigating tissue-specific mechanisms using advanced genetic tools, and exploring curcumin analogs or delivery systems such as nanoparticles or phytosomes that enhance stability and uptake (Ghosh et al., 2018). Furthermore, cross-species validation of key mechanistic targets such as SOD, mTOR, and

mitochondrial biogenesis in rodent models is essential for translational development. In conclusion, curcumin exerts potent anti-aging effects in *D. melanogaster* through a combination of antioxidant reinforcement, transcriptional reprogramming, mitochondrial preservation, stress resistance, and neural protection. Its hormetic response highlights the need for precision in dosing, and continued research will be crucial to establishing its role as a scientifically validated geroprotective agent.

2.3 Silibinin

a flavonolignan extracted from the medicinal plant *Silybum marianum* (milk thistle), is widely recognized for its potent antioxidant, anti-inflammatory, hepatoprotective, and cardioprotective properties (Polyak et al., 2010; Kroll et al., 2007). Although traditionally studied for its effects on liver function in mammalian systems, recent studies in *Drosophila melanogaster* have revealed its potential as a geroprotective agent. In this model organism, silibinin has demonstrated the capacity to delay aging by mitigating oxidative stress, preserving intestinal barrier integrity, maintaining immune homeostasis, and enhancing stress resilience (Xiong et al., 2022). Under conditions of chronic stress induced by dextran sulfate sodium (DSS) or bleomycin (BLM), dietary supplementation with silibinin at a concentration of 1 µM significantly extended the lifespan of wild-type *Drosophila*, providing protective effects in both male and female flies (Xiong et al., 2022). This lifespan extension was closely linked to the preservation of intestinal function, as silibinin-treated flies maintained the structural integrity of epithelial junctions and avoided the characteristic “smurf” phenotype, a marker of intestinal barrier failure and systemic aging (Rera et al., 2012).

Additionally, silibinin helped sustain gut acidity and normalize excretory patterns even under chemical insult, underscoring its role in protecting gut physiology (Xiong et al., 2022). Further analysis revealed that silibinin markedly reduced intestinal oxidative stress, as evidenced by a decrease in dihydroethidium (DHE) fluorescence in midgut tissues. This reduction in oxidative stress was accompanied by an upregulation of key endogenous antioxidant enzymes, including catalase (Cat), superoxide dismutase (SOD), and glutathione S-transferase D1 (GstD1) (Xiong et al., 2022). Simultaneously, silibinin suppressed the expression of various pro-inflammatory antimicrobial peptides such as *Attacin A*, *Cecropin C*, *Defensin*, and *Diptericin*, as well as inflammatory cytokines including *upd2* and *upd3*, indicating a coordinated molecular response shifting from a pro-inflammatory to a homeostatic immune profile (Wang et al., 2020). This aligns with prevailing aging theories that implicate chronic oxidative and inflammatory damage as central contributors to age-related decline (Franceschi et al., 2000). Taken together, these findings position silibinin as a promising plant-derived compound capable of delaying aging in *Drosophila melanogaster*. It achieves this through a multifaceted mechanism involving enhancement of antioxidant defenses, suppression of stress-induced signaling pathways such as JNK and Toll, improvement of proteostasis, and stabilization of gut barrier function (Xiong et al., 2022; Wang et al., 2020). Its effectiveness under chemically induced stress conditions highlights its potential relevance to age-related pathologies, particularly those involving systemic inflammation and gut dysbiosis. However, to advance its use as a therapeutic agent, future studies must focus on optimizing dosage, dissecting tissue-specific effects, and

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comparing outcomes to models of physiological aging. Ultimately, the insights gained from *Drosophila* studies can pave the way for evaluating silibinin's translational potential in mammalian systems and human aging biology.

2.4 Quercetin

is a naturally occurring flavonoid highly abundant in many fruits and vegetables, including citrus, onions, apples, grapes, and broccoli, contributing an estimated 25–50 mg/day to the average human diet (Ross & Kasum, 2002). Recognized as one of the most potent reactive oxygen species (ROS) scavengers among flavonoids, quercetin also exhibits pronounced anti-inflammatory, senolytic, and senomorphic properties by neutralizing free radicals and modulating senescence-associated secretory phenotype (SASP) factors (Kobayashi et al., 2015; D'Andrea, 2015). In mammalian models, quercetin has demonstrated the ability to promote apoptosis of damaged senescent cells and to activate autophagy-promoting signaling pathways regulated by AMPK and SIRT1/PGC-1α, suggesting a strong potential in delaying age-associated dysfunctions (Zhu et al., 2015; Russo et al., 2012). In *Drosophila melanogaster*, experimental studies support the anti-aging efficacy of quercetin, demonstrating that it extends lifespan and improves stress tolerance through several synergistic biological mechanisms (Pallauf et al., 2016; Zhao et al., 2022). One prominent effect of quercetin is the preservation of gut function and intestinal stem cell (ISC) homeostasis. By reducing oxidative stress and suppressing insulin/IGF-like signaling (IIS) within ISC populations, quercetin delays age-related gut hyperplasia and prevents barrier breakdown, while improving gut acid-base balance and facilitating recovery from chemical insults (Zhao et al., 2022). Additionally, quercetin enhances protection against environmental and oxidative stressors, including blue light exposure, hydrogen peroxide (H_2O_2), and paraquat. Under these conditions, quercetin-treated flies showed higher survival rates and sustained locomotor function (Du et al., 2020). Biochemical assays revealed a marked reduction in oxidative markers such as protein carbonyls and lipid peroxidation, accompanied by increased levels of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione (Zhao et al., 2022). Furthermore, the expression of redox-sensitive regulatory proteins like Hsp70 and *Upd1* was normalized, indicating a restored oxidative balance (Pallauf et al., 2016). Quercetin also induces a hormetic stress response, whereby short-term exposure to low doses upregulates genes involved in detoxification (e.g., *Sod1*), heat-shock proteins (e.g., *Hsp70*), and DNA repair enzymes (Russo et al., 2012). This adaptive response primes the organism for long-term resilience against stress-induced damage.

Notably, quercetin confers neuroprotective benefits as well. In *Drosophila* models of Alzheimer's disease, characterized by amyloid-beta (Aβ) toxicity, quercetin improved lifespan, motor performance, and viability (Ayuda-Durán et al., 2020). Transcriptomic analysis revealed that quercetin helped restore cell-cycle regulation by modulating key genes such as *FoxO* and Polo kinases, thereby supporting neuronal proteostasis and cellular function (Ayuda-Durán et al., 2020).

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Mechanism	Description	Representative Compounds	Evidence in D. melanogaster	Reference
Antioxidant defense	Direct scavenging of reactive oxygen species (ROS) and upregulation of endogenous antioxidants (e.g., SOD, catalase, GST) to reduce oxidative damage to DNA, lipids, proteins.	Quercetin, curcumin, caffeic acid, plant polyphenols	Quercetin delays intestinal stem cell aging by suppressing ROS-linked JNK signaling in midguts. Methanolic extracts rich in polyphenols (e.g., Platanus orientalis) lowered ROS and boosted proteasome activity.	Sun et al., (2020)
Autophagy induction	Activation of autophagy–lysosome pathways to remove damaged organelles and protein aggregates, improving cellular renewal and proteostasis.	Resveratrol, quercetin, tiliroside, chalcones	Platanus orientalis extract and tiliroside enhanced lysosomal cathepsin activity and longevity, likely via AMPK-mediated autophagy. Quercetin triggers autophagy (LC3-II upregulation). Purple sweet potato polyphenols increased autophagy markers and lifespan.	Ray et al.,(2021)
Nutrient and energy pathway modulation	Inhibition of IIS and mTOR signaling; activation of AMPK/Sirtuin/FOXO axis to mimic calorie restriction and enhance metabolic resilience.	Prunetin, ginsenosides, resveratrol	Prunetin increased SIRT1 and AMPK expression, lifespan extension, and NF-κB gene induction. Ginsenosides from ginseng prolonged lifespan ~10% via increased AMPK, FOXO, SIRT1, and suppressed TORC1/S6K.	Reiter et al., (2001)
Anti-inflammatory & immune modulation	Suppression of chronic inflammatory signaling (e.g. JNK, NF-κB, Toll) and antimicrobial peptide production, reducing inflammaging.	Silibinin, caffeic acid, acai polyphenols	Caffeic acid prevented JNK-driven intestinal stem cell hyperproliferation. Acai extract reduced JNK-target gene GstD1 under a high-fat diet. Silibinin	Peng et al., (2021)

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			downregulates antimicrobial peptides and JNK/Toll pathways under gut stress.	
Stem/progenitor cell homeostasis	Maintenance of tissue integrity by regulating proliferation and preventing premature differentiation/senescence of stem cells.	Quercetin, caffeic acid, silibinin	Quercetin maintained gut barrier and ISC regulation. Caffeic acid reduced ISC hyperplasia and preserved gut function in aging flies. Silibinin protected epithelial junctions and gut barrier under chronic toxicity.	Wilson et al. (2016)
Mitochondrial protection & biogenesis	Enhances mitochondrial function, reduces mitochondrial-derived ROS, and supports energy metabolism via AMPK/PGC-1α/SIRT pathways.	Resveratrol, quercetin, grape skin polyphenols	Platanus orientalis polyphenols recovered proteasome and mitochondrial function. Resveratrol drives mitochondrial biogenesis via AMPK/SIRT1/PGC-1α in mammalian models.	J Cell Mol Med et al.(2020)
Proteostasis & senescence regulation	Promotes clearance of misfolded proteins and senescent cells via autophagy and senomorphic/senolytic actions.	Quercetin (Bcl-xL inhibition), chalcones	Quercetin is known as a senolytic (in mammalian cells via Bcl-xL) . 4,4'-Dimethoxychalcone induced autophagy via GATA factors, delaying aging in flies.	Wg et al., (2000)
Hormetic stress adaptation	Low-dose exposure triggers adaptive stress responses (heat-shock proteins, DNA repair, antioxidants), increasing resilience.	Quercetin, luteolin, curcumin	Quercetin induced hormetic upregulation of Hsp70 and DNA-repair genes. Luteolin shown to activate SIRT3/ROS/MAPK pathways in models.	Cook et al., (2006)

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Table1: - Mechanisms of Anti-Aging Action of Plant-Derived Compounds in *Drosophila melanogaster*

Recent research has highlighted specific plant extracts with notable anti-aging effects in *Drosophila melanogaster*. A study on proanthocyanidin-rich fractions from *Tamarindus indica* demonstrated improvements in neuromuscular function and increased lifespan, suggesting potential neuromodulatory and antioxidant benefits (Paul et al., 2021). Similarly, ginger (*Zingiber officinale*) extract was found to prolong lifespan and ameliorate metabolic dysfunctions in flies, indicating its role in enhancing metabolic health (Ahmad et al., 2015). Another investigation into the effects of *Lasia spinosa* L. stem extract revealed its capability to extend lifespan through antioxidant activity (Rokeya et al., 2022). The underlying mechanisms by which these phytochemicals exert their anti-aging effects involve complex interactions with cellular pathways. Key processes include the reduction of reactive oxygen species (ROS), activation of autophagy, and modulation of gene expression related to stress responses and metabolic regulation. For example, the administration of ellagic acid in *Drosophila* led to upregulation of genes like *dFOXO* and *SOD2*, which are associated with longevity and oxidative stress resistance (Dutta et al., 2020).

Despite the promising findings in *Drosophila* models, translating these results to human health requires cautious optimism. The complexity of human aging and the influence of environmental and genetic factors necessitate comprehensive studies to validate the efficacy and safety of these compounds in humans. Nonetheless, the insights gained from *Drosophila* research provide a valuable foundation for the development of plant-based interventions aimed at promoting healthy aging.

Plant Name	**Active Compounds**	**Observed Effects in *Drosophila***	**Reference (APA)**
Camellia sinensis	Catechins (EGCG)	Antioxidant activity, extended lifespan, improved stress tolerance	Peng et al., (2009)
Curcuma longa	Curcumin	Lifespan extension, reduced ROS, activation of antioxidant pathways	Suckow et al. (2006)
Vitis vinifera	Resveratrol	Sirtuin activation, mimics calorie restriction, neuroprotective	Wood, J. G., et al. (2004)
Moringa oleifera	Quercetin, Kaempferol	Extended lifespan, oxidative stress resistance	Wankhad., et al. (2024)
Tamarindus indica	Proanthocyanidins	Increased antioxidant enzyme activity, lifespan extension	Anamik et al. (2024)
Withania somnifera	Withanolides	Stress tolerance, neuroprotection	Kumar, S., et al. (2015)
Glycyrrhiza glabra	Glycyrrhizin, Flavonoids	Anti-inflammatory, antioxidant, lifespan promotion	Shrivastava, S., & Saxena, S. (2018)
Panax ginseng	Ginsenosides	Enhanced stress resistance, improved metabolic regulation	Park, H. H., et al. (2013)

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Plant Name	Active Compounds	Observed Effects in *Drosophila*	Reference (APA)
Ananas comosus	Bromelain, Flavonoids	Improved locomotor function, lifespan enhancement	Bauddh, K., et al. (2023)
Ocimum sanctum	Eugenol, Ursolic acid	Antioxidant, thermotolerance, increased fly survival under stress	Jamuna., et al (2005)

Table 2. various active compounds and their protective effect

Future Perspectives

Advances in *Drosophila melanogaster* research have highlighted a wide range of phytochemicals—from anthocyanins to flavonoids—as powerful anti-aging agents, revealing mechanisms such as autophagy induction, antioxidant defense enhancement, and inflammation modulation (Peng et al., 2021; Pallauf et al., 2016). To translate these promising findings into practical applications for aging science, future research must focus on several key areas.

One critical direction involves holistic mapping of autophagy and apoptosis pathways. Phytochemicals such as curcumin, anthocyanins, and extracts from purple sweet potatoes have shown the ability to extend lifespan by enhancing autophagic flux and regulating apoptotic processes (Lee et al., 2010; Sun et al., 2020). Using advanced genetic reporters, such as GFP-tagged Atg8 for autophagy and Caspase sensors for apoptosis, will allow researchers to precisely quantify tissue-specific effects and establish direct links between these pathways and phenotypic outcomes like improved muscle function or delayed neurodegeneration (Zhao et al., 2022). Another promising area is the integration of precision nutrigeroscience and chronobiology. Since dietary phytochemicals modulate nutrient-sensing pathways such as IIS and TOR, aligning their administration with feeding schedules or circadian rhythms may amplify their geroprotective impact (Green et al., 2022; Katewa et al., 2016). Understanding the temporal dynamics of compound activity could significantly enhance lifespan and healthspan benefits, positioning *Drosophila* as a model for testing "when to eat" alongside "what to eat" for optimal aging outcomes.

Furthermore, synergistic strategies involving multi-compound combinations should be explored. Many phytochemicals target overlapping pathways, including oxidative stress, inflammation, and autophagy. Combinatorial assays—such as those pairing anthocyanins with curcumin, or quercetin with resveratrol—can help identify additive or synergistic interactions using isobolographic models (Russo et al., 2012; Wang et al., 2021). This approach may uncover potent compound pairs with superior efficacy compared to single agents. Structure-based optimization is also essential, given that the molecular structure of phytochemicals significantly influences their stability and bioavailability. Designing analogs such as glycosylated flavonoids or employing novel delivery systems like nanoparticles may enhance absorption and therapeutic outcomes (Ghosh et al., 2018). Such optimization efforts will be critical for advancing these compounds toward clinical utility. To ensure translatability, findings from *Drosophila* should be validated across species. Mechanistic insights—such as the preservation of intestinal stem cells by caffeic acid (Lin et al., 2021) or the suppression of inflammatory pathways like JNK and Toll by silibinin (Xiong et al., 2022)—must be tested in

Caenorhabditis elegans, rodent models, and mammalian organoid systems. This cross-species validation is crucial for confirming the conserved nature of phytochemical effects and assessing their relevance in human biology.

Finally, an emerging frontier lies in the use of phytochemicals as senolytic agents and proteostasis regulators. Compounds like quercetin and curcumin may offer the ability to selectively eliminate senescent cells or enhance clearance of misfolded proteins (Zhu et al., 2015; Ayuda-Durán et al., 2020). Using *Drosophila* models of cellular senescence and proteotoxic stress can help evaluate these capabilities, potentially extending the application of phytochemicals beyond mere lifespan extension to combatting age-associated diseases such as neurodegeneration and gut dysfunction.

Conclusion

Over the past decade, *Drosophila melanogaster* has proven to be a highly effective model organism for studying the anti-aging potential of plant-derived phytochemicals (Gáliková & Flatt, 2010; Partridge et al., 2018). Numerous naturally sourced compounds, including polyphenols, flavonoids, stilbenes, chalcones, and steroidal saponins, have demonstrated the ability to extend lifespan and improve healthspan in flies (Peng et al., 2021; Pallauf et al., 2016). These compounds exert their effects through a range of conserved biological mechanisms, such as the reduction of oxidative stress, activation of autophagy and proteostasis, modulation of nutrient-sensing pathways, attenuation of chronic inflammation, regulation of stem cell activity, and induction of adaptive stress responses (Green et al., 2022; Katewa et al., 2016).

For instance, plant extracts like *Tamarindus indica* have been shown to enhance the activity of key antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione S-transferase (GST), thereby reducing reactive oxygen species (ROS) accumulation and promoting neuromuscular health and survival (Paul et al., 2021). Similarly, extracts from *Platanus orientalis*, purple sweet potatoes, and resveratrol-rich sources have been shown to stimulate autophagy and enhance lysosomal function, contributing to improved cellular renewal and delayed onset of senescence (Sun et al., 2020; Lee et al., 2010). In addition, compounds such as resveratrol, quercetin, ginsenosides, and prunetin modulate insulin/IGF-1 and TOR signaling, while activating AMPK, SIRT1, and FOXO—eliciting calorie-restriction-like benefits that support metabolic homeostasis and stress resistance (Zhao et al., 2022; Dutta et al., 2020; Lee et al., 2009). Plant-derived agents like silibinin and xanthohumol have demonstrated anti-inflammatory activity by downregulating JNK and Toll signaling pathways and preserving gut barrier integrity, which is essential in preventing age-related inflammation and dysbiosis (Xiong et al., 2022; Liu et al., 2020). Moreover, compounds such as caffeic acid, quercetin, and silibinin maintain intestinal stem cell homeostasis, which is crucial for sustaining epithelial renewal and barrier function during aging (Lin et al., 2021; Zhao et al., 2022). These multi-targeted actions of phytochemicals reflect a synergistic mode of action that improves systemic resilience against cellular and physiological decline. Altogether, findings from *Drosophila melanogaster* studies have provided compelling evidence for the geroprotective efficacy of plant-derived compounds. The conserved nature of aging pathways

between flies and humans underscores the translational relevance of these findings. Continued research in this area should focus on unraveling specific molecular targets, optimizing compound dosages and delivery methods, and validating these effects in higher organisms through preclinical and clinical studies. Such efforts will be instrumental in advancing the development of natural, low-toxicity interventions that promote healthy aging and delay the onset of age-related disorders in humans.

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