The Neuroprotective Effects of Tea against γ-secretase Activity, APP Interactors, and tau-related Processes in Alzheimer's Disease: Insights from *Caenorhabditis elegans* Models

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***Abstract*—Alzheimer's Disease (AD) is one of the most pervasive neurodegenerative diseases worldwide, marked by brain atrophy and neuronal loss. This study focused on tea's neuroprotective effects on AD progression with the classical AD model organism *Caenorhabditis elegans* strain CL4176. Pretreatment with Zijuan Pu'er tea (ZJPT), Xihu Longjing Tea (XHLT), Jasmine Tea (JT) and Japanese Motcha Tea (JM) before Aβ production led to a significant reduction in the paralysis rate and numerical decrease of Aβ production of the CL4176 strain. Gene expression analysis revealed changes across three functional categories, with genes involved in γ-secretase activity, APP interactors, and tau-related processes. Thus, this study demonstrated tea consumption prior to Aβ production might prevent the onset of AD, probably by regulations of γ-secretase activity, APP interactors, and tau-related processes.**

***Keywords*—*Caenorhabditis elegans*, Alzheimer's disease, natural product, tea, Aβ**

I. Introduction

Alzheimer's Disease (AD) is a complex, age-related neurodegenerative disorder that affects over 30 million people worldwide [1]. It is characterized by progressive cognitive decline and memory impairment due to brain atrophy, neuronal loss, the formation of tau tangles, and the accumulation of amyloid-beta (Aβ) peptides in senile plaques [2]. Despite extensive research efforts, AD remains a significant unmet medical challenge, with only three new drugs approved for treatment between 2020 and 2023 [1]. Current therapeutic drugs for AD face limitations such as single-target mechanisms, suboptimal efficacy, and significant side effects. However, emerging research suggests that certain bioactive compounds found in tea may possess neuroprotective properties that could slow the progression of AD or mitigate its onset [3–5]. Despite these promising findings, the underlying molecular mechanisms remain largely unclear.

The etiology of AD encompasses a range of factors, including family history, gender, head trauma, other diseases, and social psychology [2]. Several hypotheses elucidate its pathogenesis, with Aβ deposition and tau hyperphosphorylation being prominent. These processes result in extracellular amyloid plaques and intraneuronal neurofibrillary tangles. In the Aβ hypothesis, a key pathological hallmark of AD involves the dysregulation of secretase enzymes, which play a critical role in Amyloid Precursor Protein (APP) processing. β-secretase and γ-secretase are responsible for the cleavage of APP, leading to the production of toxic Aβ peptides that aggregate into plaques [2]. Given its pivotal role in AD pathogenesis, β-secretase has been a major target for therapeutic intervention [6].

Traditionally, rodent models such as mice and rats have been used to study AD; however, the nematode Caenorhabditis elegans (*C. elegans*) has gained recognition as a valuable model organism in neurodegenerative disease research, including AD [7]. C. elegans offers several advantages, including a well-characterized genome, a short lifespan, ease of genetic manipulation, and conservation of key molecular pathways relevant to human neurodegenerative diseases [8]. Notably, C. elegans models of AD exhibit characteristic Aβ-induced toxicity, making them an effective platform for studying potential therapeutic compounds [9].

Tea is rich in bioactive compounds, including Tea Polyphenols (TPP), L-theanine (L-TH), tea pigment, tea polysaccharides, and caffeine [3, 4]. Epidemiological studies indicate that regular tea consumption can lower the risk of developing AD. The protective mechanisms of these tea components against AD involve multiple pathways: they reduce the production and aggregation of amyloid-beta (Aβ), inhibit tau protein aggregation and hyperphosphorylation, prevent neuronal apoptosis, modulate neurotransmitter levels, alleviate oxidative stress and neuroinflammation, and regulate the gut microbiota [10]. However, the specific genetic and molecular mechanisms underlying these effects remain to be fully elucidated.

In this study, we investigated the neuroprotective effects of tea in the C. elegans AD model. Our research

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aims to observe AD-related phenotypes and explore potential genetic pathways through which tea may exert its protective effects. Specifically, we hypothesize that tea's neuroprotective properties may be related to the modulation of γ-secretase pathways, APP interactors or tau-pathways, providing valuable insights into its potential as a preventive intervention for AD.

II. Method

A. Maintenance and Synchronization of C. elegans

C. elegans strain N2 (wild type) and CL4176 dvIs27[pAF29(myo-3/A-Beta 1-42/let UTR) + pRF4(rol-6(su1006))] were obtained from the *C. elegans* Genetic Center, CGC (University of Minnesota, Minneapolis, MN, USA) (Fig. 1). The transgenic worm strain CL4176, which expresses muscle-specific Aβ1–42, exhibits paralysis under non-permissive conditions [11]. The N2 and CL4176 strains were maintained at 16°C on solid standard Nematode Growth Medium (NGM) and fed *E. coli* (OP50) as a food source [Sydney Brenner, 1997]. All worms were synchronized to the L4 stage for maintenance and assays.

Fig. 1. N2 (wild type) and CL4176 strains.

B. Preparation of Tea Extract

Zijuan Pu'er Tea powder was obtained from the Pu'er Tianfu Biotechnology Development Co., Ltd. (Pu'er, China). Tea powder (1 g) was extracted with 50 mL of boiling water for 20 minutes. After extraction, the final volume was adjusted to 50 mL, making a tea extract with a working concentration of 20 mg/mL. The tea extract was then incorporated into OP50 bacteria on NGM plates. Prior to use, the tea extract was allowed to return to room temperature (20°C) [3].

The tea extracts examined in this study included Zijuan Pu'er tea (ZJPT), Xihu Longjing tea (XHLT), Jasmine tea (JT) and Japanese Motcha tea (JM), as shown in Table I. The working concentration of these teas were 20 mg/ml, according to the previous research [4].

TABLE I. The Groups

Groups		Drug	Working concentration
CL4176	#1	Zijuan Pu'er Tea (ZJPT)	20 mg/ml
	#2	Xihu Longjing Tea (XHLT)	
	#3	Jasmine Tea (JT)	
	#4	Japanese Motcha Tea (JM)	
	#5	None	-
N2	#6	None	-

C. Paralysis Assay

The *C. elegans* transgenic strains N2 and CL4176 were maintained at 16°C on NGM plates seeded with *E. coli* OP50, with or without added tea extracts. For the paralysis assay, worms were incubated with or without tea extracts at the permissive temperature of 16°C for 72 hours. Following this incubation, worms were transferred from 16°C to 23°C for further cultivation [4]. Paralysis was assessed at 26 and 32 hours post-shift. Worms were considered paralyzed if they exhibited head movement only or failed to move their bodies when touched with a platinum loop [12]. Paralysis rate = (# Paralyzed worms / # Total sample) × 100%

D. Aβ Aggregation Assay

After a 32-hour treatment in the paralysis assay, worms were collected in 1 mL of 1× PBS and transferred to a centrifuge tube. The worms were then sonicated and centrifuged at 14,000 rpm for 2 minutes. The resulting supernatant was transferred to a new tube for further analysis. The soluble protein concentration in the supernatant was determined using the protein assay (Thermo®), and protein concentrations were adjusted to ensure equal levels across all experimental groups. For Thioflavin-T staining, 10 μL of 10 × PBS and 2 μL of 1 mM Thioflavin-T (MACKLIN®) were added to each protein sample, adjusting the final volume to 100 μL. The fluorescence of Thioflavin-T-bound Aβ aggregates was measured using a Synergy HT Plate Reader (Thermo®), with excitation at 440 nm and emission at 482 nm. Fluorescence readings were averaged from at least three independent experiments.

E. RT-qPCR

After a 32-hour ZJPT treatment, worms were collected, centrifuged and the pellet was stored. Total RNA was extracted. RT-qPCR was performed using SYBR Green Master Mix on a (BIOER®). Target genes (*sel-12*, *hop-1*, *aph-1*, *aph-2*, *pen-2*, *feh-2*, *unc-34*, *ptl-1*, *sut-1*, and *sut-2*) were analyzed, normalized to *act-1*, and quantified. Each experiment was performed in triplicate, with statistical significance.

F. Statistical Analysis

Statistical analyses were conducted using Prism 10 software (GraphPad Software, Inc., La Jolla, CA, USA). The paralysis and Aβ aggregation data for worms cultured with or without tea were compared to the CL4176 group without tea using two-way Analysis of Variance (ANOVA). For the RT-qPCR data, statistical significance was assessed using a two-tailed, unpaired Student's *t*-test. Results are presented as the mean ± Standard Error of the Mean (SEM) from three independent experiments. *p*-values of < 0.05 were considered statistically significant, with $p < 0.05$, $p < 0.01$, and $p < 0.001$ indicating varying levels of significance.

III. Results

A. Tea Treatment Reduced Paralysis Rate in the C. elegans AD Model

The paralysis rate of wild-type (N2) worms exhibited a slight, yet statistically insignificant, increase following the temperature shift from 16°C to 23°C (Fig. 2). conversely, the CL4176 strain demonstrated a significantly higher paralysis rate (26 hr: 21.84%; 32 hr: 34.49%). Treatment with all four types of tea significantly mitigated the paralysis rate, with the Zijuan Pu'er Tea (ZJPT) group showing the most pronounced reduction (26 hr: 1.33%; 32 hr: 4.01%). These results indicated that tea confers a protective effect against AD-like paralysis in CL4176 worms.

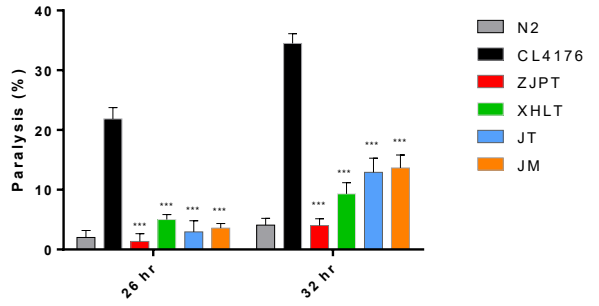

Fig. 2. Tea treatment reduced the paralysis rate in CL4176 worms. Data are presented as Mean ± SEM. *** $p < 0.001$.

B. Tea Treatment Reduced Aβ Accumulation Numerically in the C. elegans AD Model

All CL4176 worms exhibited higher ThT fluorescence levels than wild-type (N2) worms, regardless of tea treatment (Fig. 3). But when compared to the CL4176 worms that didn't get any tea, those treated with any of the four types of tea showed a reduction in ThT fluorescence levels, though the decrease was not statistically significant. Among all the groups, the CL4176 + ZJPT treatment showed the greatest reduction, at 16.8%. These results suggested that tea treatment may reduce Aβ aggregation in a numerical but statistically insignificant manner.

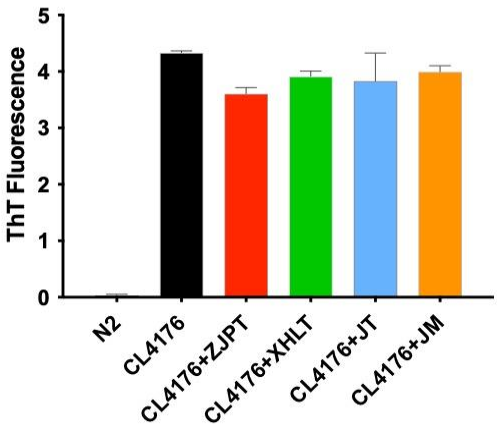

Fig. 3. Tea treatment reduced ThT fluorescence levels in CL4176 worms. Data are presented as Mean ± SEM.

C. Pathways Associated with γ-secretase, APP Interaction, and tau May Be Regulated by ZJPT Pretreatment

RT-qPCR analysis revealed changes in gene expression following ZJPT treatment (Fig. 4). Among γ-secretase components, *sel-12* expression increased, while *hop-1*, *aph-1*, and *aph-2* were downregulated, suggesting potential regulation of γ-secretase activity. APP interactors *feh-1* and *unc-34* also exhibited altered expression, with *feh-1* downregulated. Tau-related genes *sut-1* and *sut-2* were upregulated, whereas *ptl-1* expression decreased. These findings indicated that ZJPT may modulate pathways associated with γ-secretase, APP interaction, and tau regulation.

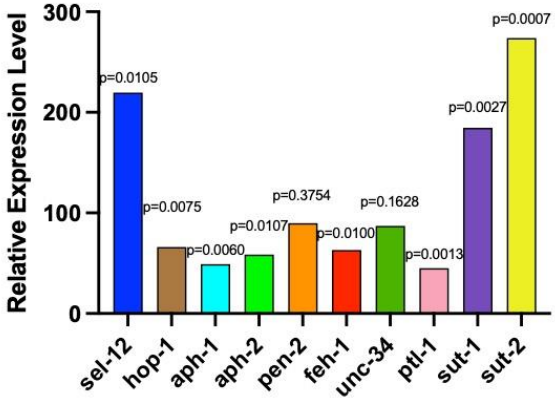

Fig. 4. Relative expression levels of AD-related genes affected by tea treatment. Data are presented as Mean ± SEM.

IV. Discussion

This study demonstrated that tea extracts significantly reduced paralysis rates in the *C. elegans* CL4176 Alzheimer's Disease (AD) model. Among the various tea assessed, Zijuan Pu'er Tea (ZJPT) exhibited the most substantial neuroprotective efficacy. Additionally, Thioflavin-T staining suggested a numerical decline in Aβ aggregation following tea treatment. Furthermore, gene expression analysis revealed that tea application modulated the expression of genes associated with γ-secretase activity, APP interactors, and tau-related components. Collectively, these findings suggested that constituents of tea may exert neuroprotective effects against Aβ-induced toxicity, thereby necessitating further investigation to elucidate the underlying mechanisms.

A. The Potential Components That Preventing AD Need Further Investigation

In this study, four types of tea demonstrated significant effects in delaying the progression of AD. The findings were consistent with previous researches and implied that various teas could inhibit the onset and progression of AD. For instance, extracts of Greek mountain tea have been shown to reduce amyloid-beta (Aβ) deposits in both CL2006 and CL4176 strains of *Caenorhabditis elegans* [13]. Similarly, *Jasonia glutinosa* (L.) DC., a type of rock tea, has been reported to reduce Aβ-induced paralysis in the CL4176 strain [14]. These results highlighted the

potential therapeutic value of tea extracts in mitigating AD-related pathology.

Identifying the specific active ingredients in tea responsible for AD prevention is of critical importance. Once isolated and characterized, these compounds could be optimized and developed into targeted therapeutics for AD. The observed neuroprotective effects of tea are likely attributable to bioactive compounds that are common across the tested teas. Polyphenols, such as catechins, theaflavins, and flavonoids, have been previously implicated in AD prevention due to their antioxidant and anti-amyloidogenic properties [15]. These compounds were known to scavenge free radicals, reduce oxidative stress, and interfere with the pathological aggregation of Aβ peptides, which are hallmarks of AD progression [15]. Among these mechanisms, the inhibition of oxidative stress has been extensively studied. For example, nematodes treated with rock tea exhibited increased resistance to juglone-induced oxidative stress [14], although basal levels of Reactive Oxygen Species (ROS) were not measured. Similar protective effects against oxidative stress induced by tert-butyl hydroperoxide and Cr^{6+} have been reported for carqueja extracts and various types of tea [16, 17].

In addition to their antioxidant properties, some bioactive compounds in tea have been found to inhibit AD through other pathways. Epigallocatechin Gallate (EGCG), a major catechin in green tea, has been shown to inhibit β-secretase [18]. By modulating this enzyme, EGCG may reduce Aβ burden and slow AD-related neurodegeneration [18]. Furthermore, theanine, an amino acid unique to tea, has been shown to promote neuroprotection by enhancing synaptic plasticity and modulating neurotransmitter balance [18]. Caffeine, another bioactive compound in tea, has been linked to reduced cognitive decline through its ability to block adenosine receptors and mitigate neuroinflammation [19].

Given these findings, further investigation is warranted to elucidate the precise mechanisms by which these bioactive compounds exert their protective effects against AD. It is also important to explore whether their synergistic interactions enhance their efficacy. Future studies should focus on bioavailability, dosage optimization, and potential long-term effects to assess their viability as pharmacological interventions against AD in mammals. Understanding these aspects will be crucial for translating the observed neuroprotective effects of tea into effective therapeutic strategies for AD.

B. The Dosage of Tea to Prevent AD Needs Further Investigation

In this study, we employed a fixed concentration of tea extract in the worm model to investigate its neuroprotective effects. The chosen concentration of 20 mg/ml tea powder demonstrated significant neuroprotective effects, suggesting a potential role in AD prevention. However, this finding prompted critical questions regarding the optimal dosage required for effective AD prevention in humans. Translating our experimental dosage to practical human intake is highly complex due to significant metabolic and physiological differences between humans and nematodes. For instance, caffeine, a major component of tea, and tea polyphenols such as catechins and theanine [18] exhibit different absorption and metabolism profiles in humans compared to nematodes. These differences make direct comparisons and dosage extrapolations challenging.

The catechin polyphenols in green tea had neuroprotective effects such as inhibition of amyloid-beta aggregation and anti-apoptosis, which suggested that green tea may have significant protective effects on AD [20]. A cross-sectional survey of 2015 subjects aged 65 or older in Eastern China found that tea consumption was associated with a low prevalence of AD and severe cognitive impairments [21]. However, the association between tea intake and AD remained inconclusive. A clinical study suggested that regular tea consumption—typically between 2 to 5 cups per day—is associated with reduced AD risk, while than 13 cups per day brought a significant risk in AD progression [22]. The potential mechanism underlying this correlation may involve the impact of caffeine intake in the tea on brain volumes. The Mendelian randomization analysis indicated that extra tea intake was inversely associated with gray matter volume and right hippocampus volume but positively associated with total brain volume and white matter volume [22]. Gray matter volume and right hippocampal volume have different brain functions. Decreasing gray matter volume was associated with lower working memory performance in AD patients [23]. Right hippocampal volume loss affected auditory verbal learning test performance in patients with AD [24]. Therefore, extra tea or caffeine intake may increase the risk of AD by reducing the working memory ability as well as language functions. Therefore, further researches on the active compounds and the intake dosage are necessary in utilizing tea to prevent AD.

If the effective dosage required for neuroprotection in humans exceeds practical daily intake levels, then relying solely on tea consumption may not be a viable strategy for AD prevention. Isolating and concentrating the active compounds from tea into standardized therapeutic formulations could offer a more effective alternative. These formulations could potentially deliver the required neuroprotective effects at practical dosages. Future research should focus on optimizing the dosage and bioavailability of these active compounds to assess the feasibility of translating our findings into human applications. This approach could pave the way for developing novel therapeutic strategies for AD prevention, leveraging the neuroprotective potential of tea compounds.

C. The Mechanism of Tea in Preventing Aβ Induced Paralysis

Although tea-treated worms exhibited lower paralysis rates, the reduction in Aβ accumulation was not statistically significant. This discrepancy suggested that the relationship between Aβ burden and AD symptoms may not be strictly linear. In mammalian models, studies

have shown that Aβ aggregation alone does not fully account for cognitive decline, highlighting the role of inflammatory responses, tau pathology, and synaptic dysfunction in disease progression. The lack of a strong correlation between Aβ reduction and improved neuroprotection in our study raises the possibility that tea may exert its effects through alternative mechanisms. Potential pathways include enhancing proteostasis by promoting protein degradation and clearance, reducing oxidative stress through its antioxidant properties, or modulating neuroinflammation by suppressing pro-inflammatory signaling [16].

In this study, three pathways were found regulated by tea, γ-secretase components, APP interactors and tau-related genes.

There was no β-secretases found in *C. elegans*, but the γ-secretase complex played a crucial role in the production of Aβ peptides, which were regarded as the central to AD pathology [25]. Gama-secretase cleaved the APP to generate Aβ peptides, with $A\beta_{42}$ being particularly fibrillogenic and prone to aggregation [25]. Mutations in genes encoding components of the γ-secretase complex, such as PSEN1 and PSEN2, were linked to Familial Alzheimer's Disease (FAD) [26, 27]. In *C. elegans*, the γ-secretase complex components SEL-12 (PSEN), APH-1, and PEN-2 were essential for viability and proper development [25]. Studies in *C. elegans* have shown that disrupting γ-secretase function led to increased $A\beta_{42}$ levels and associated toxicity, highlighting its importance in AD pathogenesis [25]. In this study, *sel-12* expression was increased after tea treatment, while *hop-1*, *aph-1*, and *aph-2* were downregulated, suggesting potential regulation of γ-secretase activity.

The interplay between tau-related genes and Aβ in AD is complex and multifaceted. The *C. elegans* ortholog of tau, PTL-1, was downregulated after tea treatment in my study. It was found sharing significant sequence similarity with human tau within the microtubule-binding repeats and involved in microtubule stabilization and is essential for proper neuronal function [28, 29]. Genetic screens in *C. elegans* have identified several genes that modulate tau toxicity. For example, *sut-1* and *sut-2* are suppressors of tau-induced neurotoxicity and were upregulated by tea in this study. SUT-1 encodes an RNA-binding protein that interacts with UNC-34/Mena/Enabled, a protein involved in cytoskeletal dynamics [30]. SUT-2, a CCCH zinc finger protein, interacts with ZYG-12, a cytoskeletal linker protein [31].

Future studies could employ these biomarkers to assess oxidative stress levels, inflammatory responses, and tau pathology in tea-treated models, providing a more comprehensive understanding of its potential therapeutic benefits.

D. Future Plan

The nematode *C. elegans* has emerged as a valuable model organism for studying the neurotoxic effects of Aβ, a key pathological hallmark of AD. The simplicity and genetic tractability of *C. elegans* allow researchers to investigate the mechanisms underlying Aβ toxicity with high precision. However, translating these findings to mammalian systems, including humans, requires careful consideration of the genetic and physiological differences between these organisms.

Previous studies have demonstrated that certain tea-derived polyphenols, such as EGCG and theaflavins, can modulate BACE-1 activity in mammalian models, reducing Aβ production and associated toxicity [32]. These findings were consistent with our observations in *C. elegans*, where tea polyphenols have been shown to mitigate Aβ-induced neurodegeneration. Additionally, epidemiological studies in humans have reported an inverse relationship between tea consumption and the risk of developing AD [33]. These studies suggested that regular tea intake may have neuroprotective effects, potentially through the modulation of BACE-1 activity and Aβ accumulation.

Despite these promising findings, several challenges remain in translating these results to human applications. Controlled clinical trials are essential to confirm whether tea polyphenols can effectively reduce Aβ pathology and slow cognitive decline in humans. These trials should be designed to account for genetic and physiological differences between individuals, as well as potential confounding factors such as diet, lifestyle, and environmental exposures. Moreover, determining optimal dosages, bioavailability, and long-term safety of tea-derived compounds will be critical for their potential development as neuroprotective therapeutics.

Therefore, while *C. elegans* offers a powerful platform for studying Aβ toxicity and the neuroprotective effects of tea polyphenols, translating these findings to humans requires a comprehensive approach. Future research should focus on bridging the gap between model organism studies and human applications through well-designed clinical trials and detailed pharmacological studies. This integrative approach will be crucial for developing effective strategies to combat Alzheimer's disease and other neurodegenerative disorders.

V. Conclusion

This study provided preliminary evidence that tea significantly prevented the onset of AD in the *C. elegans* CL4176 AD model, with Zijuan Pu'er Tea showing the strongest effect. Thioflavin-T staining indicated reduced Aβ accumulation, and gene expression analysis showed modulation of γ-secretase activity, APP interactors, and tau-related components. These results suggested that tea components may protect against Aβ toxicity, requiring further investigation. Tea extracts showed promise in mitigating Aβ-induced toxicity in AD models, but more research is needed to identify active compounds, determine optimal dosages, and validate effects in humans. Understanding how tea modulates AD pathology is crucial for developing tea-based treatments.

Conflict of Interest

The author declares no conflict of interest.

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